

CARDIFF UNIVERSITY

**Cultural Adaptation of the Fertility Status Awareness Tool to
Low and Middle Income Countries (Sudan) Using Survey,
Systematic Review and Meta-analysis and Interview
Methodologies**

Rasha R. Bayoumi
MSc Clinical Psychology

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Thesis Summary

Globally, fertility problems have severe negative consequences. In Low and Middle Income Countries (LMIC) like Sudan women especially bear the burden of the inability to achieve pregnancy and childlessness. The severity of these consequences coupled with the lack of fertility knowledge motivated the need to enhance fertility awareness in LMIC. Recently several fertility awareness tools have been developed. One such tool is the Fertility Status Awareness Tool (FertiSTAT), a short, one page self-administered tool that provides information about the signs, symptoms and preventable causes of fertility problems. This tool provides personalized risk knowledge that allows women to make informed decisions about their fertility. The FertiSTAT was developed and validated in the UK but it has utility as a cost-effective tool to enhance fertility awareness in LMIC where this simple tool could be embedded in existing (but resource limited) reproductive health services. The aim of the studies presented in this thesis was to culturally adapt the FertiSTAT to ensure that it was comprehensive in its coverage of risks and it is acceptable and feasible for use in Sudan.

The potential new risk factors for inclusion in FertiSTAT were identified through literature search, expert consultations and survey. The risk factors were subjected to systematic review and meta-analysis.

Results of the studies indicated that cultural adaptation would require cultural targeting to be inclusive of new risk factors relevant to Sudan and other LMIC and be linguistically and graphically culturally appropriate. The risk factors found to be associated with fertility problems were genital tuberculosis, HIV, bacterial vaginosis, female genital mutilation and consanguinity. Results of stakeholder meetings and patient interviews lead to recommendations about changes to language and presentation of materials to enhance acceptability and feasibility of FertiSTAT. These recommendations included the need for adding provider-administered versions of the FertiSTAT to enable cultural tailoring of

information to each user's level of literacy and cultural attributes.

An integration of all knowledge acquired from these studies lead to two adapted versions of the FertiSTAT, a flipchart and a checklist. It is anticipated that these tools can be used to enhance fertility awareness in Sudan. The studies can also be used as an adaptation protocol such that the procedural knowledge gained from adaptation in Sudan can be transferred to other LMIC. Such undertakings can potentially help improve individual and, in time, societal awareness of fertility problems with the eventual aim to prevent fertility problems, alleviate individual suffering for the most vulnerable and aid in the global efforts to promote sexual and reproductive health equity where it is most needed.

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Glossary of Abbreviations

ART	Assisted Reproductive Treatment
AIDS	Acquired Immune Deficiency Syndrome
BV	Bacterial Vaginosis
CE	Cervical Electrocautery
CSG	Consanguinity or consanguineous
D&C	Dilatation and Curettage
DHS	Demographic and Health Survey
ESHRE	European Society of Human Reproduction and Embryology
FGM/C	Female Genital Mutilation/Cutting
FMoH	Federal Ministry of Health
FSH	Follicle Stimulating Hormone
GTB	Genital Tuberculosis
HBM	Health Belief Model
HIV	Human Immunodeficiency Virus
HRP	Human Reproduction Programme
ICMART	International Committee Monitoring Assisted Reproductive Technologies
ICPD	International Conference on Population and Development
IVF	In vitro Fertilisation treatment
LMIC	Low and Middle Income Countries
MA	Meta-analysis
MCH	Maternal and Child Health Unity
MDG	Millennium Development Goals
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NR	Not reported
OR.....	Odds Ratio

PIDPelvic Inflammatory Disease
PCOSPolycystic Ovary Syndrome
RF Risk Factor
RTIs Reproductive Tract Infections
STI Sexually Transmitted Infection
TFI Tubal Factor Infertility
WHO World Health Organization
UNUnited Nations

General Introduction and Thesis Overview

Infertility is a health concern that affects individuals and communities globally. The importance of allocating resources to the research and treatment of infertility to ensure adequate knowledge, equity, and accessibility has been indicated and reinforced by the global community in such arenas as the International Conference on Population and Development (ICPD), United Nations (UN) general assembly and the World Health Organization (WHO), to name a few. “Improved reproductive health and reproductive rights via universal access to sexual and reproductive health care services...” was initially established as a Millennium Developmental Goal in 2007, and continues as a target (3.7) within the Sustainable Development Goals (UN, 2015). The World Disability Survey identified infertility as an impairment of function, and it was ranked fifth on the list of moderate-to-severe disabilities (World Bank and World Health Organization, 2011). At the 1994 International Conference on population and Development it was stated that reproductive health should include the capacity and choice to reproduce, and that it is every couple’s right to decide the number of children they wish to have. Additionally, it was mentioned that infertility prevention and treatment should be included in future action (United Nations Population Fund, 2004). The inclusion of infertility care as part of family planning services was one of the five priority aspects of reproductive health emphasised in the WHO strategy on reproductive health at the World Health Assembly in 2004 and the World Summit in 2005 (United Nations, 2004, 2005).

Research in the 70s and 80s sponsored by the WHO Human Reproduction Programme (HRP) led to an understanding of the burden of disease and the global patterns of causation of infertility (van der Poel, 2012). In the 90s WHO guidelines for the management of infertile individuals were developed, and in the decade that followed, recommendations for

stakeholders were made and focus shifted to the identification of inequity and barriers to access to care (van der Poel, 2012). The shift to focus on prevention was based on the idea that preventing Sexually Transmitted Infections (STIs), Reproductive Tract Infections (RTIs), complications from childbirth and unsafe practices would yield greater benefit especially in Low and Middle Income Countries (LMIC), than treatment (van der Poel, 2012). Despite gains in other areas of reproductive, maternal and new-born health since the millennium development goals (MDG, 1995), the WHO has found that the prevalence of infertility, and thus access to care, has changed very little over the last 20 years (Mascarenhas, Flaxman, Boerma, van der Poel & Stevens, 2012), highlighting the need to develop or update cost-effective and innovative modalities of prevention not only of infertility but of fertility problems in general. Fertility problems is a more general term that encompasses infertility defined as the inability to achieve pregnancy after 12 months of regular unprotected sexual intercourse (Zegers-Hochschild et al., 2017). The prevention of fertility problems requires efforts to enhance symptom awareness and appropriate provider screening at all levels of health care.

Global Health and Risk Factors

An understanding of global health, risk factors and fertility knowledge is necessary to understand the purpose of the current project and the activities carried out. The term global health has been defined as “an area for study, research, and practice that places a priority on improving health and achieving health equity for all people worldwide” (Koplan et al., 2009). Beaglehole and Bonita (2010) defined global health as “collaborative trans-national research and action for promoting health for all”. In the current project a combination of both definitions was used to signify that the purpose of the work was to advance health promotion efforts that aim to enhance health equity through collaborative trans-national research.

The WHO defines risk as “*a probability of an adverse outcome, or a factor that raises this probability*” (Defining and assessing risks to health, WHO, 2002). The WHO emphasises that the key to the prevention of disease and injury is the focus on risk to health. They also indicate that an individual’s perception of risk is based on values formed from the processing of information ascertained from various sources. Information is attained from the media, family, familiar and peer groups, as well as messages from scientific sources, and other past experiences (Defining and assessing risks to health, WHO, 2002). Having an understanding of reproductive issues such as the fertile period and of risk factors (RFs) impacting on fertility such as age, STIs and lifestyle factors is important in the prevention of fertility problems.

Risk factors such as STIs might have the same biological impact on the reproductive tracts of people the world over, however the prevalence and predictive factors that affect whether or not a person will contract an STI and whether they will seek treatment for it might differ globally.

A global perspective on health implies integrating education and prevention programs health risks arising in different nations due to variation in socio-cultural, environmental, institutional and economic determinants of health (Huynen, Martens & Hilderink, 2005). Evidence from narrative reviews of risk profiles from the sub-Saharan, the Indian subcontinent and the Middle East suggest that socio-economic and cultural factors in these populations affect the risk profile for female fertility problems (Leke, Oduma, Bassol-Mayagoitia, Bacha, and Grigor, 1993; Bosdou, Kolibianakis, Tarlatzis and Fatemi, 2016). Reproductive health experts concur and suggest that, owing to geographic variation in prevalence and limited quality reproductive health services, women in LMIC or in certain socioeconomic or cultural settings could be at greater risk from different factors. This complex risk profile for fertility problems in LMIC, in addition to global risks (e.g., smoking, obesity, alcohol) includes exposure to communicable disorders (e.g., HIV), poorly managed

infections owing to constrained healthcare systems (e.g., bacterial vaginosis) or reproductive events (e.g., birth), consequences of cultural practices (e.g., consanguineous marriages) or dubious use of procedures (e.g., dilatation and curettage).

The importance of preventative care in fertility health

Benefits of preventative fertility health include: educating people about true risks and dispelling myths, more cost-effective than treatment, benefit a greater number of people, more effective at eliminating the social consequences of fertility problems, could improve health status of women in other ways, and could help motivate people to use other prevention services (e.g., family planning).

Primary prevention focused on the reduction of RFs for fertility problems such as STIs, pelvic inflammatory disease (PID) and lifestyle changes, could potentially reduce the prevalence of fertility problems, improve quality of life and reduce costs to healthcare systems and individuals (Macaluso et al., 2010). Secondary prevention focused on early diagnosis and management is an effective mechanism to restore fertility (Macaluso et al., 2010). Therefore, prevention efforts should target the general population as well as health care providers at all levels of the healthcare system. The disseminating of information through awareness campaigns (e.g. provider flipcharts) about fertility health, especially the preventable causes and the use of standardized diagnosis (e.g. checklist at primary level) can potentially enhance prevention efforts for fertility problems.

Fertility Knowledge.

The lack of knowledge about the signs, symptoms and preventable causes of fertility problems could be contributing to prevalence of infertility because people do not know whether or when to seek help. It is well documented that fertility knowledge is poor in High Income Countries (HIC) (Bunting & Boivin, 2008, Bunting et al. 2013) and LMIC (Ali et al.,

2011; Bunting & Boivin 2012; Dyer, 2008). Fertility knowledge and help seeking are similar in both HIC and LMIC (Bunting & Boivin 2012; Dyer, 2008), however, the harsher consequences of childlessness in LMIC make women especially more desperate to seek help, yet this is not reflected in the numbers because of the availability and affordability of treatment options. The most commonly found consequences in LMIC include but are not limited to stigma, isolation, marital instability, violence and divorce and women usually bear the brunt (van Balen & Bos, 2010; Rouchou, 2013). Thus, a cost-effective tool that could potentially help increase awareness of factors impacting on fertility could be used to help women in LMIC.

Pennings and colleagues (ESHRE Task Force on Ethics and Law, 2009) suggested that from a rights based approach, reproductive autonomy, which is defined as the right to decide when, how many and with whom to have children, should be protected. They stated that the burden of overpopulation should not be borne by the infertile, that contraception and family planning provide a means for controlling population growth without violating anyone's rights (ESHRE Task Force on Ethics and Law, 2009). The authors also noted that limited access to and prohibitive cost of infertility treatment in resource poor nations is less likely to result in population growth. They propose that prevention in the case of fertility problems is much more cost effective and long lasting and reduces the possibility of harm even if treatment is available (ESHRE Task Force on Ethics and Law, 2009). Prevention measures include the reduction of STIs through the use of condoms and reduced high risk sexual behaviours, improving postnatal and abortion practices as well as informing the public about the impact of lifestyle choices such as smoking and obesity on fertility (ESHRE Task Force on Ethics and Law, 2009). The use of a cheap, effective tool to enhance awareness of fertility problems in a low resource country like Sudan is not only ethically justifiable but it is

also practical. One such tool is the fertility status awareness tool (FertiSTAT) (Bunting & Boivin, 2010; Bunting, Tsibulsky & Boivin, 2012).

Health Promotion

Health promotion is defined as health education combined with economic, organizational and environmental support that targets individual/group/community behaviour that is conducive to health (Green & Kreuter, 1991). The attention to the global burden of diseases and health inequalities has been augmented by the National Health Promotion and Disease Prevention Objectives and Healthy People 2010 (U.S. Department of Health and Human Services, 1991, 2000), and the WHO (WHO, 2007). The effectiveness of health education and promotion has been demonstrated in various meta-analyses and review articles. For example Aarvaa, Haesb, and Visser (1997), reviewed the literature and in their meta-analysis reported mean effect sizes for primary prevention (0.46) and secondary prevention (0.49). The authors also emphasized that a strong determinant of the effectiveness of health promotion and educational tools depended on the use of theory in the development of such tools.

In a review of the literature over the past 10 years, Noar (2006) reported on the effectiveness of health mass media campaigns. The author examined the use of design principles and theory in the development and implementation of campaigns in the reviewed studies. In addition the author also reported on how such campaigns are evaluated and what effect that has on their effectiveness. The author concluded that there is growing evidence that change in behaviours as well as health knowledge, beliefs, and attitudes can be achieved through health mass media campaigns (with small-to-moderate effect size) that are accurately targeted and well-executed (Noar, 2006). The author did not report on his search strategy but stated that although the review is not meant to be exhaustive it is representative of the

literature since the articles reviewed were obtained from a variety of international journals in different disciplines. The range and breadth of articles used in this review enhance the applicability and generalizability of the results.

The proposed mechanism of change of most educational campaigns is to change individual awareness, opinions, attitudes and behaviours. The increased level of knowledge is expected to change the individual's attitude which in turn is supposed to change their behaviour. However, the move from attitude shift to behavioural change is not always easily achieved.

Numerous systematic reviews have shown that interventions with a theoretical framework have more powerful effects than those without theoretical bases (for example, see Ammerman et al., 2002; and Legler et al., 2002). The theoretical framework on which the FertiSTAT was developed is the Health Belief Model (HBM). The HBM is a conceptual framework developed to explain and predict behaviours related to health (Rosenstock 1988, 1990). Rosenstock (1988) notes, "that the energy/motivation to change behaviour is provided by the combination of perceived susceptibility and severity, and that the preferred path to action is provided by the perception of benefits less barriers". The "cue to action" is then seen as the stimulus for action that might be internal (e.g. symptoms), or external (e.g. mass media communications, interpersonal interactions, or reminder postcards from health care providers). In order to change behaviour to reduce risk for a certain disease, cognitive appraisal is required, where people must first perceive a personal risk or susceptibility to the disease and they must perceive the disease as a serious threat (Rosenstock, 1990). According to the HBM for behaviour to change one must not only perceive personal risk but the benefits must outweigh the barriers. Personalised interventions that target the determinants associated with a particular health problem have demonstrated effectiveness in moderating harmful health effects (Champion et al., 2003). Champion et al. (2003) conducted a randomized

prospective study using a personalized intervention to study the effect of five such interventions on mammography screening adherence. The variables included in the five tailored interventions were based on the HBM, including perceived susceptibility, perceived benefits and perceived barriers. Although the sample size was large (n=773) the response rate was low (between 44-26%). The authors reported that the rate of adherence to mammogram screening was significantly greater in the intervention groups than the control group (Champion et al., 2003). The most significant change was observed in the group that was initially not thinking of getting a mammogram (from 13 to 30%). The results of this study demonstrate that tailored interventions that are theoretically designed can help increase health promoting behaviours such as cancer screening.

Fulford, Bunting, Tsibulsky & Boivin 2013 demonstrated the use of the HBM construct of perceived susceptibility in women's intentions to optimize their future fertility. The authors postulated that it is not just the lack of knowledge about causes of infertility that affects women's behaviours, but that there is also the added effect of perceived susceptibility. The authors explained that a woman is unlikely to behave in ways that protect her fertility if she does not feel susceptible to fertility problems (Fulford et.al, 2013). The authors collected data from an international online study, to demonstrate the effect of knowledge and perceived susceptibility on behaviours that can enhance the chance of becoming pregnant (i.e. help seeking and making lifestyle changes). The number of participants was 10045, they were men and women from 79 countries, trying to conceive for at least 6 months and the majority of participants were between the age of 18 and 29 (Fulford et.al, 2013). Results of statistical analysis indicated that knowledge and perceived susceptibility significantly predicted medical help seeking, and that the intention to seek help was greater when there was a suspected fertility problem. Greater knowledge also affected intentions to change lifestyle. Results also showed that the relationship between perceived susceptibility and intention to seek medical care was stronger in women who had been trying

to conceive for more than 12 months. The results of this study demonstrated that women's intention to change their behaviour to enhance the chance of pregnancy (help seeking or lifestyle change) are affected by knowledge of and feeling susceptible to infertility (Fulford et.al, 2013). The large sample size, the use of an international sample and the overall robustness of the study increases generalizability of the results.

Beyond feeling susceptible to disease and targeting information to the needs of a specific group, the personalization of health messaging to the individual's risk profile can enhance behaviour change. As demonstrated in Kok, van den Borne and Mullen (1997), the effectiveness of health educational tools was largely due to perceived quality. The quality was in turn impacted by the personalization of health messaging. Edwards et al. (2012) conducted a Cochrane review that included 41 studies that looked at whether receiving personalized risk information would alter the individual's likelihood of undergoing screening for disease. Results of the review indicated that informed decision making about taking screening tests as well as knowledge and risk perception were enhanced with personalised risk communication (Edwards et al., 2012). In addition to personalized risk culturally adapting the materials to meet the needs of the target group has been found to be efficacious (Healey et al., 2017). Finally culturally tailoring the materials to the needs of each individual is also necessary and beneficial (Kreuter & Skinner, 2000). Given that personalized, culturally targeted and tailored messaging enhances perceived quality of health promotion, an effective health education tool, should have a theoretical framework, be targeted to the population of interest, elicit a sense of susceptibility and provide personalized and tailored information. The following section describes one such tool.

The FertiSTAT

The FertiSTAT is a self-administered tool developed to increase personal awareness of RFs for fertility problems (Bunting & Boivin, 2010, see Appendix A). The tool takes women through 22 lifestyle and reproductive questions (i.e., risk indicators) to generate a risk profile and, from it, personalised (colour coded) fertility guidance. Women using the FertiSTAT tick all the RFs that apply to them. These responses generate the personalised guidance that informs them of the factors affecting their fertility and actions they could take to optimize fertility health. The function of the FertiSTAT is to assist women make informed decisions about their current lifestyle and reproductive behaviour, to take action to safeguard their future fertility and, if need be, seek timely medical advice when clear symptoms of disease are present (Bunting & Boivin, 2010).

The development of the FertiSTAT was based on an assessment of the RFs for fertility problems ascertained from a literature review, a Delphi round with fertility experts and a cross sectional validation study with fertile and infertile women (Bunting & Boivin, 2010, Bunting, 2008). PubMed was used to search for information for the literature review, in addition guidelines from National Institute for Clinical Excellence (NICE) and WHO and other specific reproductive health references were used. The literature review resulted in 31 RFs being identified and grouped into three categories: demographic (e.g. age), reproductive (e.g. menstrual cycle) and lifestyle (e.g. smoking). The precise level of exposure required to have a significant effect on female fertility potential, known as the critical threshold (e.g. number of cigarettes per day or units of alcohol per week) was obtained from the original research. These RFs and associated critical thresholds were then discussed by an expert panel. This panel comprised experts in reproductive health including medical doctors, psychologist, social worker and patient advocates. From this pool of RFs, nine were excluded for the following reasons: (a) the factor was not independent from other RFs, (b) evidence of

the effect of the factor on infertility was weak or inconsistent, (c) the factor impacted on ability to carry a pregnancy to term and not just ability to become pregnant e.g. increased risk of miscarriage, ectopic pregnancy, genetic abnormalities and/or perinatal risks and (d) non-reproductive diseases (e.g., cancer, coeliac disease) were excluded because of very low incidence or likelihood that individuals with such diseases would be informed of the effect of the disease on their fertility by the treating physician (Bunting & Boivin, 2010, Bunting, 2008).

Development of the FertiSTAT included the generation of guidance that would make the tool personally relevant. The wording and layout of the guidance section of the FertiSTAT was discussed by the expert panel and potential formats were explored. The final format was then pilot tested on 15 women in different phases of their reproductive life cycle. This version of the guidance consisted of four colour coded categories: (a) blue: trying to conceive for less than 12 months (or 6 if over 34 years) and no RFs, continue to monitor situation because fertility declines with age, (b) yellow: negative lifestyle factor, modify health habits, (c) orange: reproductive factor, discuss with doctor, (d) red: serious risks e.g. absence of periods and class A drug use, must discuss with doctor if trying to conceive.

The FertiSTAT was developed and validated in the UK and Europe, and the personalized risk profile guidance was developed according to UK reproductive health guidelines and clinical recommendations of experts from Europe, Canada and Australia (Bunting & Boivin, 2010). Using a multifactorial weighted model the FertiSTAT was shown to discriminate between medically confirmed infertile and fertile women to a high degree (i.e., 85.8%, Bunting & Boivin, 2010). The FertiSTAT was designed to also assist in public health campaigns about fertility, and has been used to that effect in Europe (e.g., Belgium “test your fertility”, de Cock, 2011).

According to the authors, the FertiSTAT is the most comprehensive fertility

awareness tool in its coverage of RFs as well as inclusion of specific critical thresholds e.g. units of alcohol and number of cigarettes (Bunting & Boivin, 2010). The FertiSTAT also accounts for the variable importance of RFs in predicting fertility (e.g. smoking vs. amenorrhea) through its colour-coded scheme (e.g., risks requiring immediate action versus risks that could be monitored until pregnancy attempted). Furthermore, the FertiSTAT takes into consideration the multiplicative relationship between RFs (e.g. age and years infertile). All these considerations lead to a more comprehensive overall guidance than other online fertility awareness tools that were available at that time. Although, the FertiSTAT was developed in 2010, as seen in Appendix B, systematic review evidence indicates that original RFs included are still valid. To date the FertiSTAT has not been evaluated or used in other settings.

Significance of Fertility Health for LMIC such as Sudan

An integral aspect of the adaptation process of the FertiSTAT was the consideration of the specific cultural differences in reproductive health. One of the main issues that needed to be addressed was that in Africa, social, behavioural and cultural factors are key contributors to infertility (Ericksen & Brunette 1996). Historically, infection was described as the leading cause of infertility in Africa; 85% (Cates et al. 1985), and 64 % (WHO, Infections, pregnancies, and infertility, 1987) of African women had infertility attributable to infection. Regional studies on infection as a cause of infertility are lacking in the literature, however, studies from different countries on specific types of infection are abound. There are various types of infection contributing to infertility, the most commonly reported in LMIC being pelvic infection due to chlamydia, gonorrhoea, bacterial vaginosis and other microorganisms (WHO 1995, Malik et.al 2006, Wessels et al. 1991, Mehanna, et al. 1995, Swasdio et.al 1996, Siemer et al. 2008, Shahzad 2012, Salah et.al 2013). Other sources of

infection include unsanitary postnatal and abortion practices and cultural practices like female genital mutilation/cutting (FGM/C) (Almoroth et.al 2005, Umeora et.al 2007, Larsen 2002). Other issues that need to be addressed include the influence and effect of religion and religious practices on fertility problems. There are a number of groups who have been working in the area of infertility within a few Arabian and Islamic nations, for example, Serour from Egypt noted that religions continue to influence behaviour, attitudes and policy-making in the Middle East (Serour, 2000, 2002). He noted that in places with poor access to health care, common preventable causes of infertility include post-partum and post-abortion infections, tuberculosis and untreated sexually transmitted infections (Serour, 2008). Other researchers like Inhorn have conducted research in the region namely Egypt, Lebanon and Iran on attitudes and acceptance of treatments that are viewed by Muslim clerics as opposing to Islamic law such as adoption and gamete donation (Inhorn 2004, Inhorn 2006). An important step in the adaptation process is the understanding of the specific cultural and reproductive features of the region generally and Sudan specifically that might be impacting on fertility.

Sudan is an LMIC with varying estimates of infertility, as low as 3% from demographic data (Larsen, 2000) and as high as 80% in clinic based studies of infertile patients (Osman, 2010; Osman 2011; Abdalla, 2011). An understanding of the patterns of infertility in Sudan is complicated by the fact that published studies used samples from infertility treatment centres. Additionally, it is difficult to draw conclusions about national prevalence rates due to the small sample sizes, lack of controls and randomization in the selection of participants in these studies. Five studies conducted in Sudan reporting on prevalence of infertility, were summarized in Table 1.1. Overall the results of these studies indicated a higher percentage of primary (range 80 to 62.4%) than secondary (37.6 to 20%) infertility. However, the methodological biases in these studies as well as the lack of large

scale epidemiological studies make it difficult to establish a true infertility prevalence in Sudan.

Table 1.1.

Published Studies Reporting on Infertility in Sudan

Study	Design	Location and Sample size	Results	Possible bias
Elussein et al, 2008	Cohort/cross-sectional (all patients seen for infertility)	Khartoum Fertility Centre, medical records n=710	62.4% primary infertility 37.6% secondary infertility	No control group
Osman, 2011	Cohort (random selection form all patients attending four primary health care centres) 2007-2009	Wad Medani City, Gezira State n=200 couples	80% primary infertility 20% secondary infertility	No control group Did not report what the patients were seeking treatment for (infertility or other)
Osman, 2010	Cohort (random selection form all patients attending four primary health care centres) 2001-2002	Wad Medani City, Gezira State	79.5% primary infertility 20.5% secondary infertility	No control group Did not report what the patients were seeking treatment for (infertility or other)
Abdalla, 2011	Cohort (random selection form patients attending primary health care centres for infertility)	Wad Medani City, Gezira State n=200	79.5% primary infertility 20.5% secondary infertility	No control group
Ahmed et al, 2009	Cohort (form patients attending hospital for renal disease and surgery)	Gezira Hospital n=194 males	55.2% primary infertility 13.9% secondary infertility	No control group No indication of how patents were selected, no control group

Khalifa and Ahmed (2012) reported on infertility in Sudan in a compendium of work with the WHO addressing barriers, access and ethical issues affecting biomedical care (Khalifa & Ahmed 2012). According to the authors, infertility now is more of a concern in Sudanese society as reflected by the growing number of private treatment clinics. They reported that there are shortcomings in the type and quality of public sector services available; where there is minimal specialized training, limited privacy, no counselling and women usually presenting alone (Khalifa & Ahmed 2012).

Reproductive health policy in Sudan.

At the beginning of this project in 2014, in the Sudanese national reproductive health (RH) policy infertility care was included under the banner of family planning services, as one component among many others. The policy stipulated that infertility care should be offered in the public health sector through primary health care facilities (Sudan national RH policy, 2010).

Pathways for the investigation of the infertile couple like those provided by the WHO manual for the investigation of the infertile couple (Rowe, 1993) or the NICE guidelines are not clearly specified in the policy or the strategy. The current Sudanese RH policy does not place infertility care as a priority nor is it one of its indicators, and provision of infertility care is not addressed in the previous RH policy. However, the MoH is updating the RH policy and infertility is to be included as one of the products in the new “10 in 5” strategy (Maternal and Child Health Unity [MCH] of the Sudan FMoH, 2017). Activities in the new strategy include: (a) desk review on RFs and management of infertility, (b) study to detect baseline burden of infertility (prevalence and availability of services), (c) develop national guidelines for detection, referral and management of infertility, (d) assess available infertility services as compared to international standards, and (e) update reproductive health services to provide infertility care independent of family planning services (MCH of the Sudan FMoH, 2017).

The Aim and Objectives of this Project

The aim of this project was the adaptation of the FertiSTAT to an LMIC such as Sudan, via assessing the suitability and comprehensiveness of 22 FertiSTAT risk indicators to the Sudanese population. The desired outcome of the project was a prototype of the adapted FertiSTAT and a protocol for the adaptation process that could be used in other LMIC.

Intermediate outcomes would be attainment of feasibility and acceptability data for the use of FertiSTAT in Sudan and the region.

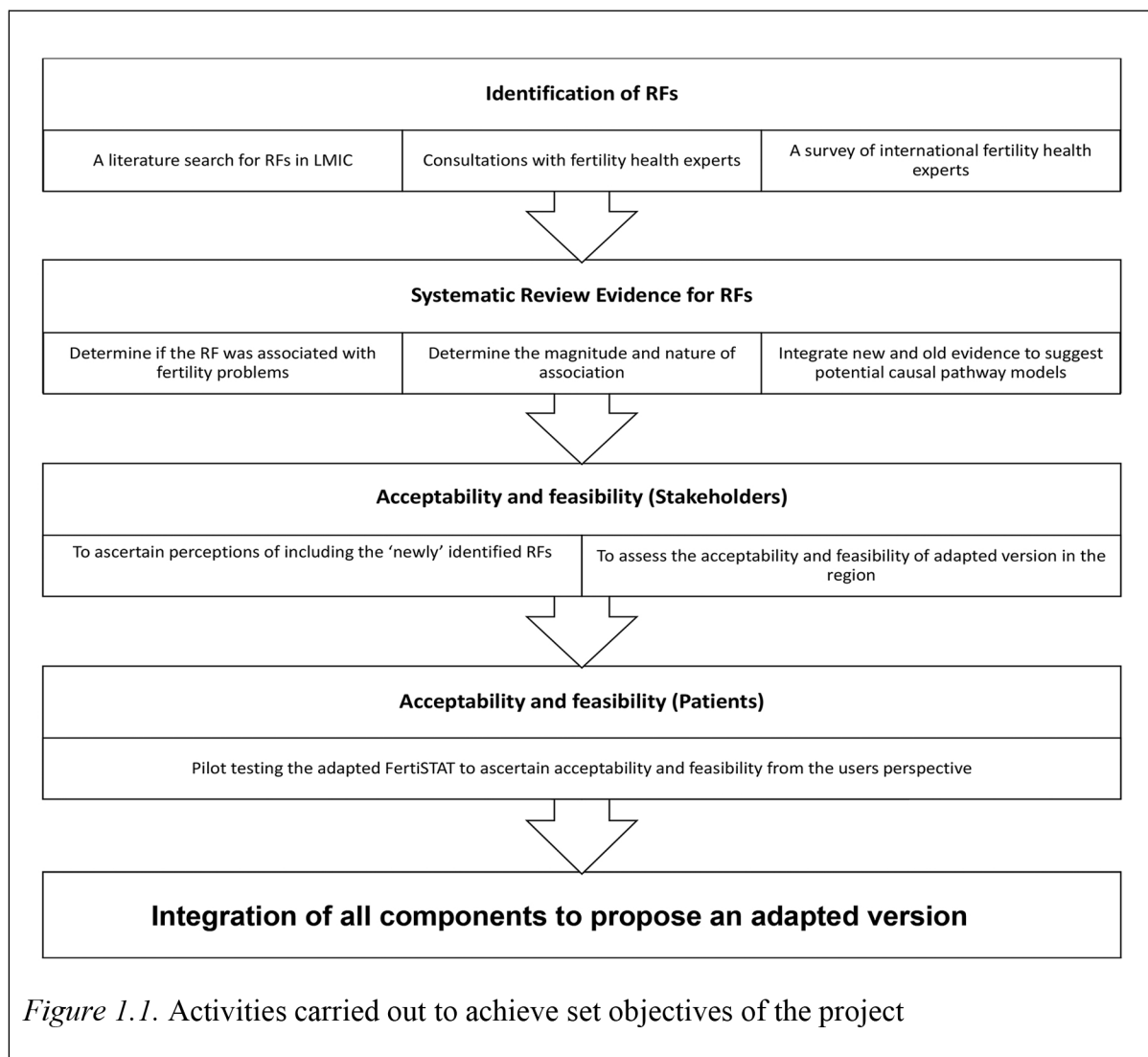
Objectives

Adaptation of FertiSTAT for use in culturally and linguistically different settings required an understanding of the differences in reproductive and cultural aspects of the intended adaptation population. This adaptation process comprised addressing the comprehensiveness of the RFs and addressing the cross-cultural acceptability and feasibility of the tool. The first objective was to evaluate whether the RFs in the FertiSTAT were comprehensive enough to suit the new context. Therefore, RFs more pertinent to LMIC including cultural practices (e.g. consanguineous marriages) and reproductive health (e.g. genital tuberculosis) were uncovered and empirically validated. The second objective was to determine the cultural acceptability and feasibility of the adapted FertiSTAT from several perspectives. Therefore, once these new RFs were included in the adapted FertiSTAT, translation and pilot testing of the adapted FertiSTAT to ensure cultural acceptability and feasibility was conducted.

Strategies to Achieve Objectives

Achieving objectives consisted of five stages, see Figure 1.1: (1) identification of RFs to be reviewed and considered for inclusion in the adapted FertiSTAT, (2) a systematic review of the literature for each newly identified RF, (3) stakeholder meetings to consider newly identified RFs and assess acceptability and feasibility, (4) pilot testing the acceptability and feasibility of the adapted FertiSTAT from the users perspective, and (5) integrating the components of all previous activities to generate the adapted FertiSTAT.

First, the identification of the RFs was done using three key activities: (a) a literature search for RFs in LMIC to generate a tentative list of new RFs, and (b) consultations with fertility health experts in the UK and in LMIC to identify other RFs not found in preceding step, (c) a survey of international fertility health experts to assess endorsement of newly identified RFs.



Second, literature on 'newly' identified RFs was systematically reviewed and where data permitted meta-analyses were conducted. There were three goals to be achieved through the systematic review, first to determine if the RF was associated with fertility problems,

second to determine the magnitude and nature of said association and finally, to integrate both new and old evidence to suggest potential causal pathway models depicting how the RF affects fertility.

Third, stakeholder meetings were conducted regionally in the Middle East and locally in Sudan. The objective of these meetings was to ascertain perceptions of including the ‘newly’ identified RFs in the adapted FertiSTAT and to assess the acceptability and feasibility of using this adapted version in the region and in Sudan from multiple perspectives mainly fertility experts. This required networking with possible stakeholders, preparing materials, holding the meetings, analysing and reporting results of the meetings. Design of FertiSTAT would then be based on incorporating results of the stakeholder meetings and the systematic review. This phase would include decisions on format (e.g., flip chart, or provider tool for Community health workers),

Fourth, acceptability and feasibility of the adapted FertiSTAT tools were assessed from the users perspective. This required pilot testing the adapted tool with potential users in Sudan, to ascertain acceptability of content and feasibility of implementing the tool in Sudan. The final products of this project would be the adapted FertiSTAT as well as the protocol for the adaptation of the FertiSTAT to other LMIC.

Finally, all the information gathered through the previous stages will be integrated to propose and design the adapted version of the FertiSTAT, to be tested on a larger scale in the Sudan in future research.

Chapter 2

Evaluation of Perceived Comprehensiveness, Feasibility and Acceptability of the FertiSTAT

General Introduction

The importance of sociocultural, geographic and economic influences on fertility and infertility has been explored in narrative reviews (e.g.: Bosdou, Kolibianakis, Tarlatzis & Fatemi, 2016; Ericksen & Brunette 1996; Leke, Oduma, Bassol-Mayagoitia, Bacha, & Grigor, 1993; Sharma, Mittal & Aggarwal, 2009). These reviews define how geography and sociocultural environments can influence the nature of RFs for fertility problems to which people are likely to be exposed. Educational efforts to improve knowledge of such risk factors should take into account the various influence on the risks presented within their tools. The aim of the present studies was to examine how such influences could be integrated into ensuring acceptability and feasibility of existing fertility awareness tools.

Recently there has been an emergence of educational tools aiming to increase public and self-awareness about fertility health. These tools seek to improve fertility awareness via websites dedicated to fertility that tailor the information visitors receive based on the risks they endorse on the site (e.g., ‘yourfertility’ website, Hammarberg, et al., 2013), public health initiatives that use self-assessment tools as a hook to attract people to sites that provide relevant fertility education (“test your fertility”, de Cock, 2011) or, more recently, fertility assessment clinics where people can have their fertility evaluated through history taking and biomedical tests (Hvidman et al., 2015; Petersen, et al., 2015). To maximize the impact of such tools globally it would be imperative to ensure that such tools are comprehensive in their coverage of RFs

and acceptable for implementation in diverse geographic and sociocultural contexts. In the present chapter, we demonstrate the process of assessing comprehensiveness, acceptability and feasibility of education materials, using the fertility status awareness tool (FertiSTAT) to be utilized within a Middle Eastern context.

The overall aims of the present studies were to determine the perceived comprehensiveness, feasibility and acceptability of the FertiSTAT among multiple stakeholders (providers and users) in settings other than the FertiSTAT development context, namely the Middle East. A mixed method approach was undertaken. The input of experts from diverse geographic locations was sought to ensure the original and adapted components were sensitive to regional and local needs (e.g., cultural acceptability, illiteracy, and wording).

Study 2.1: International survey of fertility doctors to assess the comprehensiveness of the FertiSTAT risk factors and to identify additional risk factors

Introduction

It is well known that the global distribution of disease and the corresponding patterns of health risk vary by geographic and demographic characteristics (WHO, 2009, Chapter 2). These patterns could be relevant to fertility health. Bosdou et al. (2013) examined sociocultural factors affecting female fertility in the Middle East. The results of the review showed that consanguinity, obesity, and vitamin D deficiency were risk factors prevalent in the region that could negatively impact women's fertility. The authors concluded that public health campaigns need to educate women about these potential risk factors to fertility. In an earlier review Leke et al. (1993) had also reported that there were risk factors that could be specific to a region or settings e.g. "female circumcision is an old and unhealthy practice in Africa" (Leke, et al., 1993), or malnutrition and environmental toxins in studies from Africa and parts of

South America. These narrative reviews suggested that women could be exposed to risks arising from geographic and sociocultural variations in the prevalence of medical procedures (e.g., dilatation and curettage (D&C)), cultural practices (e.g., consanguinity (CSG), female genital mutilation/cutting (FGM/C)) or communicable disease (e.g., HIV, genital tuberculosis (GTB)) that were risks not represented in the original FertiSTAT tool. The specific aim of Study 2.1 was to ascertain the comprehensiveness of the risk factors of the original FertiSTAT and to identify additional RFs to be considered during an adaptation of the FertiSTAT tool for global utility.

Materials and Methods

Participants and recruitment.

In order to build a list of global experts predominantly from outside of the UK and Europe, we obtained a list of experts active in education and training in low and middle-income countries from past Director of Medical Education, the International Federation for Fertility Societies. Additionally, information was obtained from fertility clinic websites in Africa and the Middle East in order to generate a list of 150 fertility doctors to invite to participate in the survey. Eligibility included being a fertility doctor who is currently diagnosing and treating individuals with fertility problems (e.g., obstetricians and gynecologists, OBGYN) with or without additional specialist training e.g. Reproductive Medicine (RM), Reproductive Endocrinology and Infertility (REI). Fertility doctors were invited to the survey via email and were not provided financial incentives for participation. The School of Psychology (Cardiff University) Ethics Committee provided review and approval for the project, see Appendix C.

Materials.

Study questions were embedded in an online study generated with Qualtrics (Qualtrics, Provo, UT). The questionnaire was developed specifically for the study to ascertain the

comprehensiveness of risk factors in the FertiSTAT, see Appendix D. It comprised three sections: (1) the 22 lifestyle and reproductive risk factors in the original FertiSTAT; (2) a ‘structured list’ that contained (a) medical conditions considered in the development of the FertiSTAT, and (b) proposed additional risk factors identified from literature reviews of risk factors in diverse regions; (3) open text box for participants to generate any other risk factors they felt were relevant (‘participant generated list’). Participants could indicate, for each item on the ‘structured list’, whether they felt that the item was a risk factor for impaired female fertility (yes/no). In an open text box participants were asked to provide reason(s) or justification(s) for why they would suggest inclusion of that particular risk factor in an adapted version of FertiSTAT (hereafter ‘adapted FertiSTAT’). The percentage of patients generating each risk was reported and reasons for inclusion of the risk (structured and participant generated) were categorized according to type, and their frequency reported.

Background questions were asked about country of practice, type of specialization (OBGYN, RM, REI, specific training in infertility, other specialist certification in or related to reproductive endocrinology and infertility, and/or other specialist medical training), number of years practicing as a medical doctor, as a fertility doctor, site(s) of practice (public sector, private sector, other), number of fertility patients seen per week, percentage of practice spent with fertility patients. All survey questions were marked optional.

Procedure.

Eligible participants were invited to the study via email. Those wishing to participate were instructed to click on a study hyperlink that lead them to information about the study, the consent form, and the questionnaire. At the end of the survey was a ‘submit’ button that participants clicked to submit their data.

Results

In total, 41 of 150 (27.3%) invited fertility doctors participated in the survey. The participants were predominantly from South Africa (n=10, 24%) and Sudan (n=6, 14.6%). The remaining sample included two (4.9%) participants each from Kenya, Nigeria, Uganda, Nepal, Russia, Spain, and one (2.4%) participant from each of Egypt, Libya, Tunisia, Khasikistan, Turkey, Taiwan, Paraguay, Uruguay, Panama, Belgium, UK and USA. Almost all the participants (97.4%, n=32 of 33 who responded to this question) had specialist training in addition to OBGYN training (e.g. RM or REI). Participants had, on average, 28.7 (SD= 9.4) years of practice and 19.3 (SD= 10.75) years experience as a fertility doctor. Of the 34 fertility doctors providing professional information, 50% (n=17) practiced in the private sector only, 15% (n=5) in the public sector only, and 26% (n=9) in both. A further 8.8% (n=3) practiced in other settings (e.g. academic institutions). The average number of fertility patients (or couples) managed per week was 31.58 (SD= 18.4, median= 30).

Table 2.1.1 shows percent agreement that RFs and medical conditions on the ‘structured list’ could be risks for fertility problems in women to be assessed for inclusion into an ‘adapted FertiSTAT’. The percent agreement varied between 38 and 97%, with medical and reproductive conditions (e.g., cancer, HIV) generating higher endorsement as risks than ‘practices’ (e.g., consanguinity, FGM/C). In the open text free comment section (‘participant generated list’), 25 participants suggested other medical risk factors (e.g. medications, thyroid disease), reproductive risk factors (e.g. adhesions/fibroids) or lifestyle risk factors (e.g. vitamin D deficiency, occupation/exposure). The most commonly suggested factors were related to medication or medical/reproductive conditions.

Table 2.1.1 also includes justifications for the inclusion of RFs in the ‘structured’ and ‘participant generated’ lists. In general, few participants provided a specific reason for perceiving a risk factor as a risk factor with most participants providing no justification, but this depended on the type of risk. Specifically, between 7.7% (1 of 13) and 15.4% (2 of 13) of those endorsing one of the ‘practices’ as a risk provided a justification (i.e., reduces ovarian reserve, causes recurrent miscarriage) whereas between 5.9% (2 of 34) and 34.6% (9 of 26) of those endorsing a reproductive condition reported a justification (e.g., Asherman’s syndrome, tubal damage). Uncertainty also differed between types of risk with 18.8% of people endorsing a ‘practice’ stated being unsure versus 5.9% for reproductive or medical conditions. A reason was reported for about half of the participant generated RFs, mainly for the proposed lifestyle risks.

Table 2.1.1

Percentage of participants who endorsed risk factors in structured list (1), the risk factors generated by participants (2) and principle reasons given to justify risk

Risk factors		Endorsed n/N (%)	Unsure n/N (%)	Principal reasons given to justify endorsement (n/N of responses)	No reason given n/N (%)
1. Structured list				Specific reason n/N, (%)	
Practices	FGM/C	13/24 (54.2)	2/13 (15.4)	Reduces ovarian reserve (1/13, 7.7)	10/13 (76.9)
	Consanguinity	13/26 (50.0)	1/13 (7.7)	Recurrent miscarriage (2/13, 15.4)	10/13 (76.9)
Reproductive factors	Water Pipe smoking	9/24 (37.5)	3/9 (33.3)	Reduces ovarian reserve (1/9, 11.1)	5/9 (55.6)
	Bacterial vaginosis	12/27 (44.4)	0/12 (0)	Recurrent miscarriage (1/12, 8.3); Tubal damage (1/12, 8.3)	10/12 (83.3)
	HIV	22/29 (75.9)	4/22 (18.2)	Reduces ovarian reserve (3/22, 13.6); Endometrial damage (6/22, 27.3)	9/22 (40.9)
	GTB	32/33 (97.0)	2/32 (6.3)	Reduces ovarian reserve (1/32, 3.1); Asherman's (adhesions) (5/32, 15.6); Tubal damage (7/32, 21.9); Endometrial damage (3/32, 9.4)	14/32 (43.8)
	Post-abortion infection	34/36 (94.4)	2/34 (5.9)	Asherman's (adhesions) (7/34, 20.6); Tubal damage (10/34, 29.4); Endometrial damage (2/34, 5.9)	13/34 (38.2)
	Post-partum infection	28/30 (93.3)	2/28 (7.1)	Asherman's (adhesions) (7/28, 25); Tubal damage (7/28, 25); Endometrial damage (2/28, 7.1)	10/28 (35.7)
	Repeated D&C	26/30 (86.7)	1/26 (3.8)	Asherman's (adhesions) (9/26, 34.6); Cervical damage (1/26, 3.8)	15/26 (57.7)
	Cervical electrocautery	14/25 (56.0)	0/14 (0)	Endometrial damage (1/14, 7.1); Cervical damage (2/14, 14.3)	11/14 (78.6)
Medical Conditions*					
	Diabetes	26/35 (74.3)			
	Kidney disease	22/32 (68.8)			
	SLE (lupus)	25/34 (73.5)			
	Sickle cell anaemia	16/32 (50.0)			
	Cancer	32/37 (86.5)			
2. Participant generated list			Unsure n/N (%)	Specific reason (n/N, %)	No reason given n/N (%)
Medical	Medications (pharmaceutical, psychotropic or traditional)	3/25 (12.0)	0/3 (0)	Toxins (3/3, 100)	0/3 (0)
	Male factor (e.g. cancer treatment)	6/25 (24.0)	0/6 (0)	Reduced male fertility (6/6, 100)	0/6 (0)
	Thyroid disease/treatment	7/25 (28.0)	0/7 (0)	(0/7, 0)	7/7 (100)
	Anaemia	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)

	Risk factors	Endorsed n/N (%)	Principal reasons given to justify endorsement (n/N of responses)		
			Unsure n/N (%)	Specific reason n/N, (%)	No reason given n/N (%)
Reproductive	Autoimmune diseases	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
	Cushing's syndrome	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
	Chronic liver disease	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
	Inflammatory Bowel Disease	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
	Adhesions/fibroids	2/25 (8.0)	0/2 (0)	Tubal damage (2/2, 100)	0/2 (0)
	Vaginitis	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
	Dyspareunia	1/25 (4.0)	0/1 (0)	Reduced coitus (1/1, 100)	0/1(0)
	Pelvic tuberculosis	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
Lifestyle	Pregnancy-related infection	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
	Hyperprolactinemia	1/25 (4.0)	0/1 (0)	(0/1, 0)	1/1 (100)
	Low vitamin D	1/25 (4.0)	0/1 (0)	Poor oocyte quality (1/1, 100)	0/1 (0)
	Occupation/exposure	3/25 (12.0)	0/3 (0)	Male factor (3/3, 100)	0/3 (0)
	IUD	2/25 (4.0)	0/2 (0)	Risk of PID (1/2, 50)	1/2 (50)
	Extreme exercise	1/25 (4.0)	0/1 (0)	Reduction in pulatile GnRH release (1/1, 100)	0/1 (0)
	Undernutrition/anorexia	1/25 (4.0)	0/1 (0)	(0/1, 0)	0/1 (0)
	Vaginal lubricants	1/25 (4.0)	0/1 (0)	May be spermicidal (1/1, 100)	0/1 (0)
Anal sex	1/25 (4.0)	0/1 (0)	Increases risk of Prostatitis (1/1, 100)	0/1 (0)	

Note. *Participants were not asked to provide reasons for these medical conditions. Sample size varies by question, n = number responding affirmative; N = number responding to question; NR = not reported; Unsure = participant indicated not knowing how risk factor affects fertility; FGM/C = female genital mutilation/cutting; GTB = genital tuberculosis; D&C = dilatation and curettage for any reason; SLE = Systemic lupus erythematosus; IUD = intra uterine device; PID = pelvic inflammatory disease.

Discussion

The main findings were that the RFs included in the original FertiSTAT were not perceived to comprise a fully comprehensive list of RFs applicable to several participant's country of practice. Specifically, 44% to 97% of an international sample of fertility doctors primarily from Africa and the Middle East endorsed the inclusion in an 'adapted FertiSTAT' of additional RFs arising from infection or communicable (e.g., HIV, GTB, postpartum infection) and non-communicable (e.g., diabetes, lupus) diseases. A smaller percentage, 38% to 54%, endorsed risks arising from cultural practices (e.g., FGM/C, water pipe smoking). It is not clear from the present study whether the inclusion of the risks would be justified. It is also not clear whether the difference observed between willingness to endorse cultural versus medical or reproductive types of risk is justified. Nevertheless, it can be inferred from our survey that there could be RFs not currently included in the original FertiSTAT that would need to be examined to achieve a more global understanding of RFs for fertility problems to which women could be exposed in the Middle East.

The variation in endorsement across types of risks (medical, cultural) could reflect the reality that less endorsed risks (i.e., associated with cultural practices) are actually less risky for fertility than the communicable or non-communicable risks endorsed. Alternatively, it could be that evidence about these cultural practices and their impact on fertility is either not robust, or that the evidence has not yet been adequately communicated to or accepted by fertility doctors. Additionally, the fact that more participants reported a reason/justification for the 'reproductive' RFs than for the cultural 'practice' risk factors, and that justifications were in line with those provided in existing literature on causal mechanisms suggests better knowledge of the mechanisms of action of 'reproductive' risk factors most likely due to medical training and

clinical expertise. However, we could not fully evaluate knowledge levels for mechanisms of action because the majority of participants did not provide a justification for endorsing a risk.

In the original FertiSTAT medical conditions were excluded on the grounds that within the UK and Europe, it was expected that the general practitioner or disease specialist would have informed patients affected by these diseases or disorders of the associated potential risk to fertility (Bunting & Boivin, 2010). However, results of Study 2.1 suggested that not all participating fertility doctors knew about the fertility effects of medical conditions examined, for example, 14% did not agree that cancer could be a risk for fertility problems. This suggests that at least some doctors might not inform patients of the effects of cancer on fertility. A systematic review that postdates the original FertiSTAT showed that approximately a third of cancer survivors surveyed, did not recall being told about the effects of cancer or its treatment on their fertility or reproductive potential (Tschudin et al. 2010). Together these findings would suggest that certain medical conditions should be integrated in the ‘adapted FertiSTAT’, possibly more so within settings where there is limited access to universal health care, or where there is inadequate adherence to, or lack of best practice guidelines in reproductive care.

The main limitation of the study was the low survey response rate, however it is known that when surveys are received without prior notice as was the case in our study, the response rate is approximately 20% (Kelly, Clark, Brown & Sitzia, 2003). Another limitation was that the majority of participants are highly experienced fertility doctors working within the private sector. However, the development of fertility health services is mainly based within the private sector in the countries surveyed (IFFS Surveillance, 2016; Sullivan, et al., 2013). Therefore, patients whom these fertility doctors treat could be representative of the typical patient seen in general practice, but it is possible that patients accessing private practice could differ in risk exposure,

access to overall quality health care, and type of fertility risk exposure than that observed in patients who must rely only on the public health care sector.

Future research should aim to review and synthesise available data on these additional RFs not previously included in the original FertiSTAT, and, in due course, to generate prospective data on effects of identified risks such that evidence-based information can be used to inform existing and future fertility awareness tools. Even with evidence based and RFs integrated, the international effectiveness of awareness tools might nevertheless be compromised if it is not feasible to integrate them because the tools or the topics themselves are not perceived to be acceptable to new audiences.

Study 2.2: Assessing the feasibility and acceptability of implementing an adapted FertiSTAT in the Middle East among multiple stakeholders

Introduction

Public health efforts assess the prevention of disease through addressing distal (e.g., unprotected intercourse with multiple partners) and proximal (e.g., pelvic inflammatory disease) RFs in targeted interventions such as education and awareness activities (Ezzati, et al, 2006, Chapter 4). The effectiveness of addressing risk factors through health campaigns and educational tools has been demonstrated (Noar, 2006). The implementation of evidence-based educational tools about RFs developed in one country into another country raises several issues. First, practicality (i.e. how can the materials best be disseminated e.g. setting and target audience) and acceptability (i.e. are the topics covered culturally appropriate) of the educational tool need to be determined. Second, public health campaigns designed to educate people about risk factors need to use a language of communication (wording) that is not only effective but that

is culturally appropriate. Given these issues, it is therefore imperative that feasibility and acceptability of using educational tools such as the FertiSTAT, outside the context of development, need to be examined prior to direct dissemination and implementation.

The aim of Study 2.2 was to consult with multiple stakeholders in the Middle East (as a potential target population) to evaluate perceptions of including additional risk factors identified in Study 2.1 in the ‘adapted FertiSTAT’ and to examine the feasibility and acceptability of using this adapted version in the region. A stakeholder is an individual or group with an interest in or affected by an organization or process (Partridge, Jackson, Wheeler & Zohar, 2005). A stakeholder meeting brings together the relevant stakeholders in a structured interactive process to generate collective understanding, joint decision making and courses of action (PMNCH & WHO, 2014). They are used in various fields from corporate to healthcare, and are usually conducted to involve stakeholders in the development or implementation of a program. The involvement of stakeholders enhances adherence to recommendations, increases the credibility of findings, reduces distrust, increases awareness and leads to support and advocacy for the program (Salabarría-Peña, Apt, & Walsh, 2007). In healthcare the relevant stakeholders include: policy makers, healthcare professionals, institutions, non-governmental organizations (NGOs), national and international societies, researchers, academics, technical experts, donors and users (PMNCH & WHO, 2014). Steps involved in conducting a stakeholder meeting include: (1) identifying the relevant stakeholders, (2) choosing a facilitator(s), (3) designing the dialogue process, (3) preparing the logistics and (4) holding the meeting (PMNCH & WHO, 2014). The data generated are then subjected to qualitative data analysis and it is anticipated that the process will facilitate implementation efforts.

Materials and Methods

Participants and recruitment.

Two separate meetings were held in the Middle East. The first was held in Egypt at the Middle East Fertility Society (MEFS) annual conference on 04/11/2016. The MEFS administration identified, and then emailed 30 fertility doctors, practicing in the Middle East and planning to attend the MEFS conference in order to invite them to the study. Of the 30 invited, 28 (93.3%) agreed to participate and 21 (75%) were able to attend the group meeting facilitated by RB and SvdP, while 7 (25%) participated in individual meetings with the facilitators, at a later time on the same day of the group session. The second meeting was held in Sudan under the guidance and leadership of the National Reproductive Health Program (NRHP) of the Sudanese Federal Ministry of Health (FMoH) on 03/12/2016. The NRHP sent invitations to representatives from policy-makers, women's and youth groups, service providers, UN, users (patients), local experts in qualitative research methodologies and group collaboration in Sudan. Of the 15 invited, 11 (73%) were able to attend the meeting facilitated by RB and JB. The invitations for both sets of meetings stated that the meeting agenda would be regarding the comprehensiveness of the 'adapted FertiSTAT' and the feasibility and acceptability of its use it in the Middle East.

Materials and procedure.

Prior to the meetings, the facilitators were advised by international experts that the use of a self-administered tool in the Middle East might not be feasible given educational levels. Therefore, the authors developed two versions of the tool. A flipchart version appropriate for use with patients of lower literacy and a checklist version appropriate for fertility doctors to administer with their patients who could not complete the FertiSTAT on their own. The flipchart is one of the methods the World Health Organization (WHO) and other NGOs such as the

Population Council would use at the level of primary care in regions of lower literacy when communicating reproductive health issues between health care providers and their clients (e.g., to provide education on contraception, WHO, 2005, Department of Reproductive Health and Research). The flipchart version of the FertiSTAT was based on the WHO family planning flipchart (WHO, Department of Reproductive Health and Research, Decision-making tool for family planning, 2005). It has a two-sided page format, with one page facing the client and the other facing the provider. The page facing the client depicts information about risk using pictures and simple graphics; the flip page faces the service provider and displays corresponding key questions, detailed information and discussion points for the provider to educate the client enabling informed choice and understanding of the reproductive issue of interest. The checklist version of the FertiSTAT is a two-part tool, with a list of signs, symptoms and risk factors for men and women that could be beneficial for settings where circumstances may not permit use of a flipchart. Checklists are increasingly used to efficiently condense a large quantity of information, describe essential evidence-based criteria, and enhance the objectivity and reproducibility of communications between practitioners and patients, including settings where there is low literacy (Hales, Terblanche, Fowler & Sibbald, 2008). Checklists can also stimulate reliable information-gathering and provision (Hales, et al., 2008). Both versions (flip chart, checklist) included the 22 original FertiSTAT items, as well as the additional risk factors identified in Study 2.1. The section for men was based on the factors included in the original FertiSTAT, however an update of risk factors impacting on male fertility was beyond the scope of the current thesis, nevertheless this area should not be neglected in future research.

During all meetings, information regarding FertiSTAT development, validation and applicability in the UK and Europe, as well as information about the additional risk factors

identified in Study 2.1 and the two versions of the tool were presented to the participants. The presentation was followed by discussion of the comprehensiveness, applicability, feasibility and cultural/regional acceptability of the original FertiSTAT items and the additional risk factors. Discussion also included specifics of implementation e.g. target audience, setting, practicality of use such as format most suitable given level of education and wording appropriate to the cultural and religious confines of the region. Due to the sensitivity of the topics discussed, recording devices were not utilized, however detailed notes for the first set of meetings were taken by Svdp and RB, and by a Sudanese research assistant for the meeting in the Sudan.

Data analysis.

RB and Svdp conducted thematic analysis (as coders) (Braun & Clarke, 2006). The thematic analysis steps followed were: (1) familiarisation with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes and (6) producing the report (Braun & Clarke, 2006). Coders derived codes from the meeting notes through inductive coding. Codes with the same meaning (e.g., “population of interest” and “target population”) were combined together. Coders discussed and reached agreement on whether each code communicated a unique meaning or fit with other existing codes. Each coder organized codes into main themes independently and these were discussed between coders to deepen the analytic process, enhance trustworthiness of the findings and to ensure the cohesiveness of each theme and consistency with the overall meanings in the dataset. Sub-themes within the main themes were also identified to facilitate understanding and presentation of the results. Participant quotes were used to illustrate meanings. The use of parentheses within quotations indicates text added for clarity, while omitted text is represented using the following: (...). Illustrative quotations are from fertility doctors, unless otherwise specified.

Results

The attendees of the first meetings at the MEFS conference were fertility doctors practicing in ten countries in the Middle East (Algeria, Egypt, Iraq, Jordan, Lebanon, Libya, Saudi Arabia, Sudan, Syria and Turkey). The attendees of the second meeting were stakeholders from Sudan including representatives from: the Ministry of Health, medical societies (Sudanese Society of OBGYN and Sudanese Reproductive Health and Embryology Society), reproductive health experts from UN agencies, national NGOs, previous patients, epidemiologists, medical doctors from local universities (University of Khartoum, Ahfad University, National Ribat University) and fertility doctors practicing in both the public and private sectors. As shown in Table 2.2.1 thematic analysis resulted in five main themes, which are described in detail in the next section.

Table 2.2.1

Themes that emerged from thematic analysis of data gathered from both meetings

Theme	Summary of theme
Need for fertility awareness in the Middle East	Fertility awareness was endorsed based on societal emphasis on childbearing and widespread fertility misconception of information
Content acceptability and specific tool changes	The content of the FertiSTAT found to be acceptable. The wording of certain items was found to be unacceptable or acceptable if modified to be more culturally sensitive.
Target audience	Suggestions for the appropriate age and marital status of the target audience included: couples preparing for marriage, newly-married couples and young unmarried individuals. Suggestions about subcultures e.g. refugees as separate target audience were made.
Setting for implementation	Macro level settings: disagreement about the possibility of a regional tool Micro level settings: urban and rural settings may have different needs. Possible settings for implementation include: schools, primary healthcare facilities, infertility clinics (tertiary level), community and media.
Need for further research (setting specific) and a working group	Next steps require setting up a working group to finalize the content of the material and oversee necessary regional research Areas for future research: identify settings and target populations, identify which format would be suitable for which setting, field-testing the wording used to communicate sensitive and stigmatized topics to determine acceptability and alternatives, evaluate research to ensure highest possible quality of research (empirically sound), ethical problems e.g. screening will lead to huge demand and services need to be available

1. Need for fertility awareness in the Middle East.

It was stated that fertility awareness was necessary and timely, “there is a niche for such tools especially because our societies are geared towards childbearing”. There is a lack of knowledge about when to seek medical advice, reflected in patients seeking treatment “too early or too late”, indicating a lack of awareness. It was also noted that there is a lack of “information about risk factors” or “misconception about what is a risk.” It was indicated that knowledge about when to seek advice, risk factors and the signs and symptoms of fertility problems would help “reduce the burden” on healthcare systems and individuals, as well as to potentially reduce the prevalence of known preventable causes of infertility e.g. time to treatment and age: “if they know when to get help” and “they don’t know what age (decline in fertility starts)”. The social stigma of infertility was highlighted especially for men (...) “they (men) deny having the problem because it is shameful, makes him less of a man” and a previous patient agreed: “male infertility is a stigma”. Another issue highlighting the need for fertility awareness was the misconception of information accessed by patients from the internet: “the main problem is the internet, where individuals look up on say polycystic ovary syndrome (PCOS) and immediately find infertility as the end”. It is known that 80% of PCOS patients have either infertility or an extended time to pregnancy, however managed PCOS decreases this risk (Balen et al, 2016).

2. Content acceptability and specific tool changes.

There were two acceptability sub-themes that emerged (a) acceptability of the content, and (b) acceptability of the wording. There was consensus that the original content, the medical conditions and the additional risk factors e.g. FGM/C were necessary for a Middle East version of the FertiSTAT: “yes it’s (original FertiSTAT) good but you need these (medical conditions, and additional risk factors) others”, and that “with some adjustment to the language” the

‘adapted FertiSTAT’ could potentially be culturally acceptable and used in the Middle East.

Several participants also noted the absence of PCOS from the ‘adapted FertiSTAT’, stating that it was common in their practices: “30% of my patients have PCOS”.

There were conflicting opinions regarding wording. Some suggested that it was necessary to make specific changes to the wording of some items in the ‘adapted FertiSTAT’ due to sensitivity of specific topics, most notably, use of illegal drugs and unprotected sex with multiple partners. Some suggested certain risk factors should be removed, altered or only communicated to specific audiences (e.g. married couples only):

“Some items (drugs and sex) are not acceptable and we cannot ask questions so openly like this.”

“Sex with multiple partners is unacceptable in a community of husbands and wives (...) the word ‘partner’ particularly should not be used.”

“Items regarding things like multiple partners need to be delivered in a sensitive manner (...) use ‘extramarital affairs’ or ‘previous relationships’ (...) but you have to ask.”

A reproductive health expert from a Sudanese NGO added the importance of the behaviour of the provider who would be asking about these risk factors: “you have to be careful when asking these women (...) your body language, choice of words”.

However, others felt that the ‘adapted FertiSTAT’ tools could be used as is in their countries or clinic settings. Most of the terminology was “comprehensible” but “medical terminology like endometriosis and PID (pelvic inflammatory disease) should be replaced with more understandable terminology, which would require deliberation at length and with several

experts”. Some also felt that wording/phrasing might need to be “country specific (...) or specific to subcultures (within countries)”.

3. Target audience.

Three target audiences were specifically suggested for the ‘adapted FertiSTAT’ tools, namely young unmarried individuals, couples preparing for marriage and newly-married couples. A difference in opinion about possible target audiences was observed. For example, a reproductive health expert from a Sudanese NGO suggested that the materials should “target couples who are about to get married”, a representative from a UN agency in Sudan noted that “school children (and) university students are the main targets” and fertility doctors noted the following:

“Young adults preparing for marriage (...) thinking about having children are most primed to receive (educational) information about their current and future fertility”.

“You can’t talk about these things (sex) with people who are not married yet (...) that’s not acceptable (...) it is only acceptable for all formats (of the ‘adapted FertiSTAT’) to be delivered to married couples.”

“Times are changing and in some places it is now more acceptable to do (educational materials) with younger unmarried people. Younger generations are more accepting of such things (sex and drugs).”

“Yes, yes adolescents and unmarried young adults (since) there is a shift in attitudes towards sensitive topics.”

It was suggested that “the tool (‘adapted FertiSTAT’) can be integrated” into existing programs that target young adults like the “premarital counseling for young adults (...) young

couples' premarital counseling package". For example, one fertility doctor stated that premarital counseling is "mandatory about certain medical disorders such as HIV and hepatitis B and C to receive a marriage certificate in Egypt". In Sudan, it was suggested by a representative from a local university that the 'adapted FertiSTAT' could be integrated into the "free youth workshops held by the Ministry of Youth, targeting couples who are about to get married and educating them about things like family planning, HIV testing".

Within this main theme there was also the possibility of targeting subcultures, which referred to "unique subcultures within each country that may have different needs and level of understanding (...) acceptability" that need to be explored. For example: refugees "who despite their circumstances are very keen on having children and the need for fertility awareness is acute" in this group. A suggestion was made about a potential target audience for testing of the tools: "these tools should be tested at community level targeting the general population, for example via media campaigns."

4. Setting for implementation.

The fourth main theme concerned the setting for implementation of fertility awareness tools with sub-themes: macro and micro level settings. There was overall agreement that "it ('adapted FertiSTAT') can be implemented without great difficulty in specific setting(s)". At the macro level there were suggestions that there should be a regional level tool, "a Middle East version" that was tailored to the needs of that specific region. However, others disagreed: there "cannot be a regional tool" and we "cannot (even) have a country tool" and "a regional tool may not be possible but a national tool would be beneficial". The main reason given for why a macro level tool would be difficult to implement was diversity of people within the region or a country and the exposure to different risks e.g. FGM/C highly prevalent in Sudan and Egypt but almost

non-existent in Lebanon and Oman. The fertility doctors made the observation that even within each country, different settings could have different needs, for example there may be a “need to develop a rural and an urban version for each country”, a reproductive health expert from a Sudanese NGO made a similar suggestion, emphasizing the difference in literacy levels across the country that may affect understanding of the questions and the application of the tool to guide behaviours.

At the micro level, discussions lead to the suggestion of several settings for use and dissemination including schools, primary health care facilities, infertility clinics (tertiary level), media and community. There was agreement that the primary care level setting would help reach the widest audience, but diverse opinions were expressed about fertility awareness education in schools. Several fertility doctors expressed an opinion that the school setting (regardless of age of pupils) would not be appropriate due to the sensitive issues raised (e.g., sexual activity and illegal drug use) although not all fertility doctors agreed, as some felt that adolescents were already exposed to these issues. Others, including an epidemiologist and representatives from Sudanese NGOs, expressed the view that “integrating the material in the curriculum of schools and universities would be best”. This was further reinforced by ongoing activities for example that in Sudan the “Ministry of Health and Ministry of Education with the support of UNICEF are in the process of rolling out (in schools) an adolescent health module on fertility, targeting ages 10-19 years”. It was stated that “interventions have to start early (...) first place should be at the school, train the teachers, give the information to the educators”. There was consensus that further research was necessary to ascertain acceptability and utility in schools, and if and how to target different adolescent and young adult age groups.

Opposing views were expressed regarding the utility of using the tools with patients attending infertility clinics. Participants expressed the view that “all my clients are infertile and this (‘adapted FertiSTAT’) would be useless (at this stage)”, while others stated that “we get many (patients) who are NOT infertile, but they think they are, so it (‘adapted FertiSTAT’) would be very helpful” in identifying those who indeed required medical attention. The use of media such as TV, radio, internet and social media (e.g. Facebook, WhatsApp) was discussed as potential viable dissemination platforms in both meetings. It was suggested that in Sudan the material could be disseminated in group format rather than one-on-one, for example “village meetings, community gatherings, rather than individuals” or via print media “in clinics, outpatient departments, magazines”. A representative from a local university suggested taking advantage of existing health promotion programs like the “rural extension program at Ahfad University”, which sends students to the villages to deliver health education messages within these rural communities. Midwives and health visitors were also suggested as potential providers who could be trained to disseminate this information, since they are the “main care providers in rural areas where 80% of deliveries are at home”. The demographic characteristics of participants (e.g., education, socioeconomic status) were perceived to possibly necessitate the use of “different tools/formats for different settings”. For example, the provider flipchart would be useful for settings where individuals have lower education, the checklist would be helpful within a fertility care clinic or centre, while a self-administered questionnaire would be suitable only for settings where potential users are “well educated”.

5. Need for further research (setting specific) and a working group.

More research was thought to be necessary for updating the FertiSTAT prior to implementation within the Middle East. The MEFS experts thought that the creation of a

working group that could “finalize the content of the material” and oversee necessary regional research was the logical next step for implementation of the ‘adapted FertiSTAT’. In addition, research was needed to ensure the assignment of blue, yellow, orange or red flags for new risk factors, and further prospective testing in multifactorial models to detect how these factors would alter prediction compared to the original FertiSTAT factors was perceived to be essential to ensure appropriate guidance or referral. It was noted that the “integration of fertility awareness tools and research regarding testing different formats” would require the involvement of “professional societies” and “public health experts who would be more able to advise on where within existing healthcare services the tools can be integrated and what level of content (difficulty)”. Five main areas that were perceived to require further research prior to implementation were acknowledged. First, identify settings and target populations that would be most receptive and for whom the tool would have the most impact. Second, identify which format would be suitable for which setting, a “flipchart should be tested at primary care level” and a “screening tool (checklist) can be tested at secondary (general OBGYN) or tertiary level (specialist infertility clinic)”. Third, field-testing the wording used to communicate sensitive and taboo topics, to determine if acceptable and if not, what the more acceptable alternatives are. Fourth, identify mechanisms to ensure or evaluate reports to generate the highest possible quality of research conducted using the FertiSTAT. One participant stated that ‘the research needs to be well-coordinated and implemented (...) one bad application or extreme negative outcome could potentially destroy the whole project for example one person saying it’s inappropriate for the region or our people’. There was agreement that the research also needs to be empirically sound, requiring “systematic reviews and proof of principle for a model for adaptation” including research design for pilot testing of tools (e.g., population of interest, sampling), and a detailed

methodology to support research protocols used for any adaptation process. Finally, there was concern that “this project can be very complex, the aim of the educational program is prevention through screening programs however when that (the screening) starts (and may identify risks to or fertility problems), there will be a huge demand that may cause an ethical problem, you have to provide services or a referral pathway to cope with the demand generated by the screening”.

Discussion

Fertility doctors from various countries within the Middle East supported the use of an ‘adapted FertiSTAT’ that included the additional risk factors, in their practices and communities. There was an overall positive attitude regarding feasibility and acceptability of implementing the ‘adapted FertiSTAT’ in the Middle East. However, some concerns were expressed about wording, how the provider would approach questions and certain risks, appropriate target audiences and implementation settings that would need to be resolved through implementation research. The consensus about the need for educational campaigns to help increase awareness about fertility based on region specific research echoed recent recommendations that educational tools should include all additional risk factors (Bosdou, et al., 2016). Perceptions of participants were in line with published accounts of prevention and treatment of infertility and importance of investigating region-specific risk factors in the Middle East (Serour, 2002; Bosdou, et al., 2016) and other regions (see Leke, et al., 1993).

Although there was an overall acceptance of the original FertiSTAT items, the original FertiSTAT was not perceived to be comprehensive due to the omission of risk factors relevant to the Middle East (e.g., FGM/C, CSG) and its exclusion of medical conditions (e.g., diabetes, cancer, PCOS) as was found in Study 2.1. Additionally, there was concern about appropriateness

of wording and taboo topics (e.g., drugs, unprotected intercourse with multiple partners) for some Middle-Eastern countries, and appropriate target subpopulations within countries e.g. adolescents, unmarried individuals, requiring further exploration. The discussion made clear that what was “appropriate” was reference to social conventions about the discussion of taboo topics with different members of a community. Social norms are a powerful driver of medical health care seeking especially in low and middle-income countries (Finlayson & Downe, 2013; Thaddeus & Maine, 1994). However, hesitation could also be due to the significant penalties or shame of engaging in illegal activities e.g., alcohol use (Islam and Alcohol, 2012) in Muslim countries. Together violation of social or legal norms would indicate that divulging exposure to some risks could be very problematic for individuals, but also could place medical doctors in a compromised legal position by learning about them. Implementation research including qualitative studies could help identify how best to integrate fertility awareness tools in specific communities taking into consideration the diversity of views on wording, target audiences and setting.

Although there was agreement that the additional risk factors are necessary for a regionally (macro level) adapted tool, it was noted that further research was essential to accumulate empirical evidence on the risk factors and their impact on fertility, and to test the regional applicability of a version of the adapted tool at national or sub-national level, all of which would require a ‘working group’ to ensure all aspects are adequately researched before implementation. The generalizability of data gathered in primary research about a specific risk factor, for example, may not extend beyond the context in which it was conducted (Ezzati, et al., 2006, Chapter 4). Therefore, risk profiles need to be examined in light of context differences

between countries, or a meta-analysis across countries could be considered as necessary next steps.

Generally, the strength of involving multiple stakeholders is that they can provide unique insights, assist with implementation and ultimately lead to increased consensus for the program. Specifically, the meetings were well attended with a diverse group of participants from the Middle East. However, the main limitation is that the results may be region specific and would require testing in other regions and countries to ascertain global applicability and comprehensiveness. Another limitation is that if the stakeholders' recommendations are not heeded this can lead to unmet expectations, distrust and ultimately hamper implementation efforts. Therefore, follow through on recommendations is imperative.

General conclusion

Findings from Study 2.1 and 2.2 indicated that the process of adapting the FertiSTAT could be improved through the inclusion of medical conditions (e.g. diabetes) and risk factors arising from culturally influenced practices (e.g. FGM/C, consanguineous marriages), preventable infectious disease (e.g. HIV and GTB) and medical procedures (e.g. D&C). Before the adaptation process can be fully implemented, existing research should be evaluated to determine to what extent the proposed additional risk factors have been associated with fertility problems. Additionally, appropriate wording, target audience and settings for implementation need to be investigated. Such evaluations should provide foundational knowledge to guide the type of research needed to improve gaps in knowledge (e.g. risk imposed by endocrine disrupting chemicals) and enhance comprehensiveness and utility of the FertiSTAT.

The process of globalizing the FertiSTAT and similar tools requires more implementation research validating their predictive value across countries and demonstrating their use in such settings. However, the *processes* used in the present studies concur with cross-cultural adaptation guidelines that recommend consultations with health experts from the target population before implementation (Guillemin, Bombardier & Beaton, 1993; Beaton, Bombardier, Guillemin, & Ferraz, 2000). *Globalizing* health awareness through the adaptation of fertility awareness tools (including FertiSTAT) should aim to ensure recognition of diversity in opinion of experts and advisors with the aim to accommodate the needs of the end-user.

Chapter 3

Systematic review and meta-analyses of new risk factors for fertility problems in women

General Introduction

The WHO has made a compelling case for the importance of understanding and addressing exposure to risk as a public health initiative (World health report 2002). The impact of reducing burden of disease by targeting distal and proximal risk factors through tailored prevention programs applied to communicable and non-communicable disease could potentially be applied to fertility problems. Macaluso and colleagues (2010) suggested that the burden of infertility could be reduced by applying a public health approach that is focused on primary prevention of modifiable risks such as STIs (Macaluso et al., 2010).

Research thus far suggests that women in low resource countries may be facing unique threats to their fertility. These risks should be taken into account in the adaptation of fertility education and awareness materials. Since the FertiSTAT was developed and tested only in the UK, there may be risk factors (RFs) that are population specific that are not included in this tool. To facilitate the use of FertiSTAT (and similar tools) in LMIC, the comprehensiveness of RFs in the tool must be determined to ensure it covers likely risks in LMIC. Possible risks could be selected through a systematic examination of the literature for specific RFs relevant to the intended LMIC population, country or region and then determination of pooled estimates (i.e., meta-analysis) where possible. However, not all risks identified in this way warrant deeper evaluation and meta-analysis. Frameworks to understand the global burden of disease have criteria that can be used for the selection of risk factors (Ezzati et al., 2002). To the authors knowledge, there are no standardized criteria used to select risk factors for disease. However, similar considerations to identify global risks for disease have been used by the WHO (World Health Report, WHO, Chapter 2, 2002) and

Ezzati et al. (2002). The first consideration is to determine if the RF is potentially among the primary causes of disease, globally and regionally. If this is unlikely then consider whether the risk can be prevalent and hazardous, or highly concentrated amongst a specific sector e.g. Female Genital Mutilation/Cutting (FGM/C) can be as high as 98% of women in countries like Somalia (UNFPA-UNICEF, 2014). The second consideration would be to assess whether there is a probability of causality based on aggregate of interdisciplinary scientific information. The third consideration would be to determine if data on risk levels and exposure is available or easily extrapolated. The final consideration is to determine if the risk is potentially modifiable. Such considerations help ensure that risks submitted for deeper study and analysis are likely to be relevant for the disease of interest.

In the present thesis, RFs that might be unique to fertility problems in low resource settings were ascertained from available research, a survey of fertility doctors and discussions with experts in the field of infertility working in low resource countries (see Chapter 2). The RFs identified and endorsed were: consanguinity (CSG), FGM/C, genital tuberculosis (GTB), HIV, dilatation and curettage (D&C), cervical electrocautery (CE), vitamin D deficiency and water-pipe smoking. The considerations used by the WHO (World Health Report, WHO, Chapter 2, 2002) and Ezzati et al. (2002) for the selection of RFs were applied to the identified RFs and summarized in Table 3.1.

Table 3.1.

Application of Considerations for the Selection of Risk Factors, as well as Identification and Endorsement Attained in Previous study in this Project (Chapter 2)

Risk Factor	Primary causes of disease	Prevalent or hazardous^a	Potential causality	Data on exposure available	Potentially modifiable	Found in search in LMIC^b	Endorsed by experts in survey^c
CSG	No	Yes	Yes	Yes	Yes	Yes	Yes
FGM/C	No	Yes	Yes	Yes	Yes	Yes	Yes

Risk Factor	Primary causes of disease	Prevalent or hazardous^a	Potential causality	Data on exposure available	Potentially modifiable	Found in search in LMIC^b	Endorsed by experts in survey^c
HIV	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GTB	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BV	No	Yes	Yes	Yes	Yes	Yes	Yes
D&C	No	Unknown	Yes	No	Yes	Yes	Yes
CE	No	Unknown	Unknown/ anecdotal	No	Yes	Yes	Yes
Vit D def	Yes (musculoskeletal)	Yes	Yes	Yes	Yes	Yes	Yes
Water pipe smoking	Yes (smoking in general)	Yes	Yes	Yes (smoking and equivalence to smoking)	Yes	No	Yes

Note. Considerations from: Chapter 2, World Health Report, WHO, 2002; Ezzati et al., (2002). ^aEzzati et al., (2002) suggest that when the risk is not a primary cause of disease, consider the prevalence and or hazardous nature of the RF. ^b Was the RF found in the preliminary search of the literature reported in Chapter 2. ^c Was the RF endorsed by fertility experts in the survey reported in Chapter 2. CSG = consanguinity; FGM/C = female genital mutilation/cutting; GTB = genital tuberculosis; BV = bacterial vaginosis; D&C = dilatation and curettage; CE = cervical electrocautery, Vit D def = vitamin D deficiency.

In the present chapter, the validity of these RFs as predictors of fertility problems was submitted to deeper analysis examined in a series of systematic reviews (and where possible meta-analyses) using the operational definitions of fertility problems and RF applied in the original development of FertiSTAT (Bunting & Boivin, 2010). The overall aim of the reviews conducted in this Chapter was to determine if the newly identified RFs (Table 3.1) were associated with fertility problems (ability to become pregnant, to have a live birth or the time taken to achieve either) as this would determine whether or not the new risk indicator should be integrated into the adapted FertiSTAT. The present chapter describes the conceptual and methodological issues related to this aim, and how these differ from the approach taken in the development of the original FertiSTAT.

I. Operational Definitions for Fertility Problems

The FertiSTAT is used to determine the risk for fertility problems. Fertility problems could be considered from several perspectives. There are three dimensions that characterise definitions of fertility problems in the literature. The first is based on the fertility outcome, which is either an inability to become pregnant or an inability to produce a live birth. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the WHO updated the 2009 glossary of 87 terms relevant to medically assisted reproduction (Zegers-Hochschild et al., 2009) and now includes 283 terms (Zegers-Hochschild et al., 2017). In the updated glossary, the clinical definition of infertility is: “a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person’s capacity to reproduce either as an individual or with his/her partner” (Zegers-Hochschild et al., 2017). Live birth is defined separately as “the complete expulsion or extraction from a woman of a product of fertilization, after 22 completed weeks of gestational age; which, after such separation, breathes or shows any other evidence of life, such as heart beat”. However, live birth is not used in the definition of infertility, implying that an inability to achieve pregnancy rather than to produce a live birth is the defining feature of infertility. In a recent systematic review on the definition of infertility, it was reported that definitions are discipline based; epidemiologist and clinicians use a definition based on ability to achieve pregnancy, while demographers tend to define infertility as ability to produce a live birth (childlessness or absence of children) (Gurunath, Pandian, Anderson & Bhattacharya, 2011).

The second dimension that characterises the definition of fertility problems is the duration of exposure to unprotected intercourse required before infertility is declared. Depending on the preferred outcome (pregnancy, birth, childlessness) duration of exposure is operationalized as ‘time to pregnancy/birth’ or ‘time trying to achieve pregnancy/birth’ or

‘duration of childlessness’. The latter incorporates duration of lack of pregnancy, lack of live birth and duration of being without a (another) child. The duration of exposure is the interval of time during which the couple are assumed to be having unprotected sexual intercourse before pregnancy or birth occurs, respectively. As noted, the ICMAART and WHO glossary uses a period of 12 months, but a duration of 12 or 24 months has been used by clinicians to express time to pregnancy, while five or seven years of childlessness has been used by demographers (Gurunath, et al., 2011). These time frames of 12, 24 months or five years are not arbitrary but originate from the likelihood to become pregnant over time. Evers (2002) used a mathematical model to model the exposure period required for pregnancy among the most fertile to the least fertile couples (developed by te Velde, Evers & te Velde, 2001). According to the model 100% of couples referred to as “superfertile” would have become pregnant by 6 months, 93% of “normal fertile” couples would have become pregnant by 12 months (100% by 24 months). By five years 95% of the “moderately subfertile” and 45% of the “severely subfertile” would also have become pregnant. This model thus provides an expected time band for pregnancy for the range of fertility from the superfertile to severely infertile. According to the model, 12 months gives couples with normal to high fertility a reasonable chance to become pregnant while five years gives all who can reasonably be expected to be fertile this opportunity. Clinicians want to intervene as soon as subfertility can be detected therefore define infertility in relation to the point at which most couples would have become pregnant (i.e., 12 months’ duration of trying to become pregnant). Demographers want to detect fertility problems after the longest period of exposure expected to detect the capacity to reproduce and therefore tend to use the five-year period of exposure (Gurunath, et al, 2011).

The third, and final dimension to consider in defining fertility problems is the time span that encompasses the period of infertility. Current prevalence refers to the individual

presently experiencing the infertility (however defined) whereas lifetime prevalence refers to probability that an individual will have had the disease at some point in their life up to their present age (Rothman, 2012). Lifetime prevalence depends on present age and should not be confused with end of reproductive life prevalence. End of reproductive life for women is the end of the fertile phase where she is no longer able to produce biological offspring and is marked by menopause (Eunice Kennedy Shriver National Institute of Child Health and Human Development, 2013).

In the original literature search used for the development of the FertiSTAT, the search terms used were fertility and infertility (Bunting & Boivin, 2010). The same terms were used in this review as well. These search terms yielded the following outcomes: ‘risk of infertility’ defined as lack of conception after 12 months and/or a medical diagnosis of infertility (e.g., tubal factor infertility); ‘time to pregnancy’ defined as the number of months needed to achieve pregnancy; reduced ‘conception rate’ defined as a reduced chance of clinical pregnancy; ‘menstrual irregularities’ defined as short (<21 days) or long (>35 days) menstrual cycles and/or sporadic or unpredictable periods; and ‘specific diagnosis’ which were defined as a medical diagnosis of a reproductive disorder (e.g., pelvic inflammatory disease, endometriosis).

Outcomes yielded from the search that were related to reduced post-implantation ability for a live birth (e.g., gestation and delivery difficulties) were not included in the original FertiSTAT due to the number of these factors, existing awareness tools for such problems e.g., the ‘Antenatal assessment tool’ (NICE, National Collaborating Centre for Women’s and Children’s Health, 2008) and the Pregnancy and health profile: A screening and risk assessment tool (March of Dimes, 2016) and the fact that these risk indicators are routinely addressed during prenatal care (Bunting & Boivin, 2010).

Outcomes yielded from the search that were relating to live birth or childlessness were included in the current study because studies from low resource settings tend to use demographic definitions of fertility and related outcomes (e.g., childless, live birth) rather than clinical outcomes (e.g., pregnancy). Including only pregnancy outcomes might therefore have missed important risk indicators hidden within the broader fertility outcomes present in demography. Moreover, measuring the effect on pregnancy and live birth can enable specification of where in the reproductive process the RF exerts its impact. This is especially relevant for less established RFs where it is unclear how the RF affects fertility (e.g., CSG, FGM/C). Therefore for this chapter and the adaptation of the FertiSTAT, the broader term ‘fertility problems’ was used and was operationally defined as inability to achieve and sustain pregnancy and achieve desired family size.

II. Use of systematic review methodology

In the development of the FertiSTAT a narrative literature review was used to identify RFs (Bunting & Boivin 2010). An RF was considered a potential risk if at least one study reported an association between the RF and fertility problems. In the present study a systematic review methodology was applied and, where possible, meta-analyses were conducted.

The reason to adopt systematic review methodology lies in the fact that decision making in all aspects of health care needs to be informed by the best research evidence available (CRD; Centre for review and Dissemination, 2008). However, the available evidence can be weak or conflicting owing to primary research that is biased, flawed, context specific or suffers from other methodical inconsistencies (CRD, 2008). Therefore, it becomes difficult to know which evidence is most reliable or applicable to a specific situation. Systematic review offer a solution to these shortcomings in primary research, because they

evaluate and summarise all the available evidence (CRD, 2008). Additionally, combined effects estimates can be pooled to provide more precise and reliable approximations of the effect of an intervention or exposure. In this way, a thorough and transparent systematic review allows for defensible conclusions to be made, and can help identify gaps in knowledge and research that can then be addressed more consistently and rigorously in future research (CRD, 2008).

To ensure robustness of systematic review methodology and resultant findings, the data collection, analysis and presentation of findings of the reviews conducted in the present Chapter were conducted as per best practice guidelines presented in the Centre of Review and Dissemination's guidance for undertaking reviews in health care (2009) and the Critical Appraisal Skills Program (CASP; Critical Appraisal Skills Program, 2017). Notable aspects of best practice are now discussed as relates to the reviews in the present Chapter.

According to best practice for meta-analysis, the search should be focused solely on one of the outcomes as the primary outcome (e.g., inability to conceive or childless for more than 5 years). However, the research base on current RFs is not voluminous and there is significant diversity in the outcomes of primary studies reporting on fertility problems (e.g., time to pregnancy, childlessness). Therefore, such a strategy would risk ending up with insufficient studies. Accordingly to adapt the FertiSTAT the search strategy involved searching broadly for studies that included the RF and the words fertility and infertility. Inclusion and exclusion criteria were then applied to ensure the studies would provide relevant data on the relation between the specific RF and fertility problems. Each search included all possible outcomes but not all searches yielded data on all outcomes. As a result each review examined all the outcomes tested in the primary studies for that risk but these did not necessarily comprise all outcomes that defined fertility problems across the set of reviews. Therefore, pooled estimates were calculated separately for different outcomes

because combining outcomes (e.g., inability to become pregnant with inability to have live birth or with likelihood of having amenorrhea) would not be informative. Indeed, different outcomes could reflect problems in different parts of the reproductive system (e.g., damage to ovaries or uterus) or different points in the reproductive process (e.g., pre-pregnancy, gestation).

III. Use of Bradford Hill criteria to evaluate causality between RFs and fertility problems and inform final selection of risk factors

In the original FertiSTAT development study the risk factors identified in the literature were presented to and discussed with 25 fertility and reproductive health experts to determine which risk factor should be included in FertiSTAT. Included factors were those that experts considered had reliable evidence and were independent of each other. In present adaptation of FertiSTAT the Bradford Hill criteria were used to evaluate the causal nature of the relationship between new RFs and ‘fertility problems’. The Bradford Hill criteria are an example of guidelines used to aid in making causal inferences from epidemiological research by exploring the strength and consistency of available evidence (Fedak, Bernal, Capshaw & Gross, 2015), through the use of the nine criteria shown in Table 3.2. In a recent evaluation of the application of the Bradford Hill criteria to current epidemiology, Fedak and colleagues (2015) defined the criteria to be valid and useful when establishing causation. The updated evaluation of the criteria (Fedak et al., 2015) determined that these criteria were still applicable with added integration of data from molecular level research to determine causation.

Table 3.2.

Bradford Hill Criteria and Definitions

Criteria	Definition
1. Strength	A larger associations indicates that causality is more likely, but a small association doesn't mean there is no casual effect
2. Consistency	The consistency of findings across different studies in different populations and settings, but also molecular level studies bolster the epidemiological evidence from observational studies, decreasing the need for repetitions of observational studies
3. Specificity	A causal relationship is more likely if the association between a factor and the effect is more specific
4. Temporality	The cause has to occur before the effect
5. Biological gradient	The presence of a dose-response (more exposure-more effect) relationship increases the likelihood of a causal relationship
6. Plausibility	The biological evidence provides a model that helps explain the association of interest
7. Coherence	Consistency between laboratory and epidemiological findings increases likelihood of a causal relationship, similar to 'consistency'
8. Experiment	Evidence from experimental manipulation such that cessation of exposure leads to decrease in disease lends strong support to causal relationship
9. Analogy	Considering the effect of similar factors

Note. Definitions derived from Hill, 1965; Fedak et al., 2015

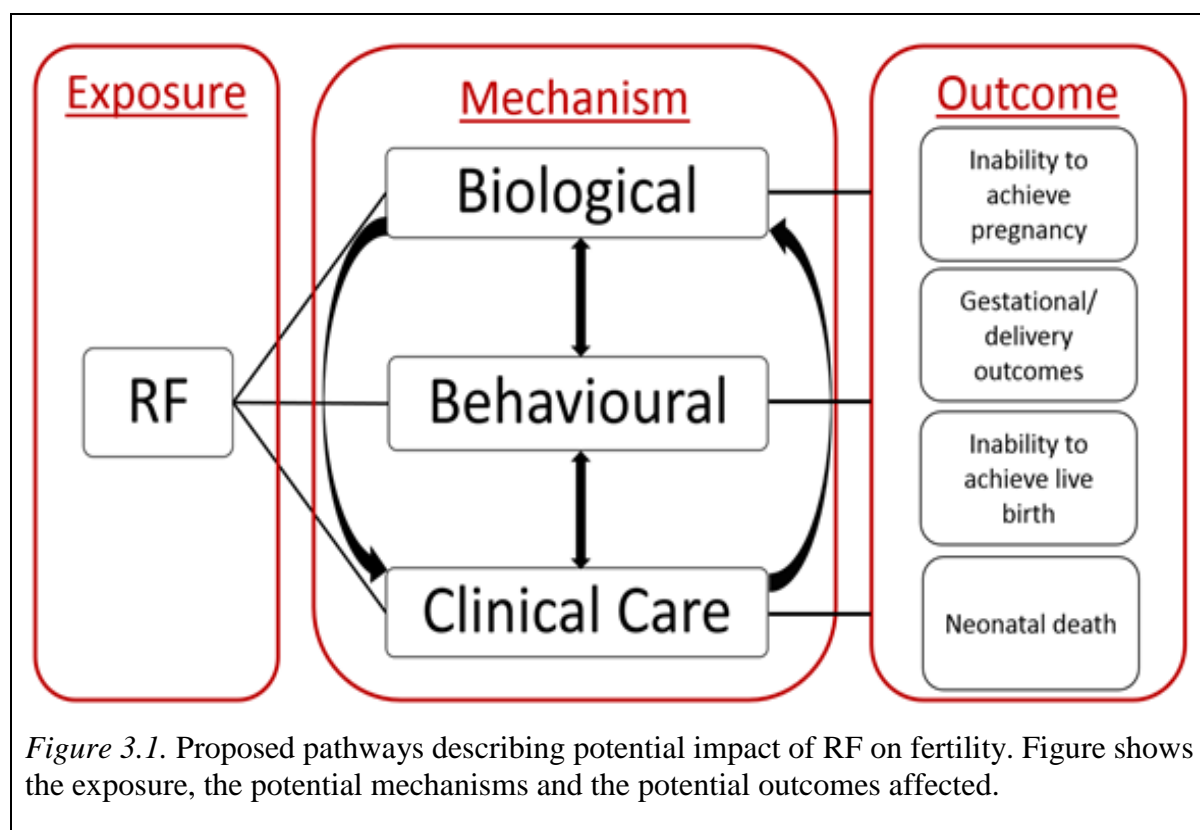
Randomized controlled trials (RCTs) are the gold standard and often believed to be the most effective and robust research design because they attempt to reduce all biases that can invalidate results and can therefore be used to make inferences about causality (Barlow, 2003). However, they are not always practical or ethical especially with risk research (Mann, 2003) such as the current research. Therefore, in the current Chapter the effect of the RFs on fertility was ascertained from pooled estimates of observational studies. The inclusion of observational studies only limited the determination of an exact causal relationship. Therefore, in the absence of RCTs, the evaluation of the causal nature of a relationship can be enhanced by applying the Bradford Hill criteria to the evidence. For example, an integration of the results of the meta-analyses conducted in the present Chapter with existing epidemiologic and molecular level evidence, can also be used to further determine causality as per criteria 6, 7 and 8 (Table 3.2).

IV. Visual representation of proposed pathways

The consideration of causality implied in the Ezzati selection criteria and the Bradford Hill criteria presented a need to clearly propose how RFs were considered to link to fertility problems. Diagrams depicting proposed pathways describing potential impact of RF on fertility were developed to depict these associations, to help identify gaps in the literature and to guide recommendations for future research. The diagrams were derived from the body of past research and the results of narrative and meta-analyses conducted in the present Chapter.

Figure 3.1 shows the general form of these diagrams. These diagrams illustrate the proposed pathway between exposure and fertility health, namely exposure to the RF, the potential mechanisms involved in its effect and the fertility outcomes associated with exposure to the RF in the available literature. This is the generic template that was modified for each risk factor. Exposure is defined as per Porta (2014, p. 104): “the variable whose causal effect is to be estimated”. Mechanisms are the potential pathways via which exposure leads to the outcomes (e.g. exposure to sexually transmitted infections [STIs] can lead to the inability to achieve pregnancy via tubal damage). More distal risk factors, such as education or socio-economic status are not shown on the figure, as the overarching aim of this thesis was to understand the effects of the novel risk factors identified for examination in this study. The potential mechanisms shown in the diagrams are informed by an aggregation of the information available in the best quality reviews in the literature. Biological mechanisms refer to changes or effects to physiology or anatomy (e.g. contracting an infection or the formation of scar tissue). Behavioural mechanisms refer to an effect on the actions people take as a result of the exposure (e.g. abstaining from sex after exposure to HIV). Clinical care mechanisms refer to the clinical care required due to the exposure (e.g. obstetric care will change for a woman with Female Genital Mutilation/Cutting [FGM/C]).

Outcome is the consequence of the exposure, defined as “all the possible results that may stem from exposure to a causal factor” (Porta, 2014, pp 206). In this study, outcomes are markers of fertility problems as present in available studies and can include an inability to achieve pregnancy, gestational or delivery problems, an inability to achieve live birth or neonatal death.



V. Overall Aim of all Systematic Reviews

The main aim of the present reviews was to determine whether the investigated factor should be included as a new RF in the adapted FertiSTAT for use in LMICs. For the intent of this review the influence of a RF on any dimension of fertility that leads to reduced pregnancy or reduced live births was included under the umbrella term ‘fertility problems’, and outcomes indicative of ‘fertility problems’ (e.g., being childless, episode of infertility) obtained from primary studies were noted. Therefore, RFs shown to be associated with poorer fertility on any of these outcomes (e.g., lower likelihood of pregnancy, longer

time to live birth, diagnosis of tubal factor infertility) were considered for inclusion in the FertiSTAT. Therefore, an RF found to impair ability to become pregnant would be included in the adapted FertiSTAT, whereas if the effect were limited to impaired ability to have a live birth it would not be included in the adapted self-administered FertiSTAT but will be used to inform comprehensive educational awareness programs such as a flipchart based on FertiSTAT.

VI. General Method for all Systematic Reviews and Meta-analyses

Guidelines such as the Centre for Reviews and Dissemination (CDR, 2008) were used to develop methodology for the current systematic reviews. The CDR recommends checking for an existing review addressing the research question before undertaking the current review. If such a review is found then its quality should be evaluated systematically using established checklists or criteria (CRD, 2008). The Guidelines recommend that evaluation should include determining whether a well-defined research question guided the review, the methodology used was comprehensive, rigorous and well reported, there was no bias in the assessment of primary studies, data extraction and synthesis, and the review process was transparent and reproducible.

Using these guidelines the following strategy was adopted for all RF reviews in the present chapter. Figure 3.2 illustrates the strategy. A systematic search was conducted using the relevant terms. If the search identified reviews published less than five years previously then these were evaluated using the “Critical Appraisal of Systematic Reviews” (WHO, Abalos, Carroli, Mackey & Bergel, 2001). If the review met quality criteria then it was summarized in the current review and upheld as the most valid evidence for that risk factor. If a review was not identified or an existing review was of poor quality or published more than 5 years previously then standard systematic review methodology was followed. Specifically,

Figure 1. Flowchart showing the decision making process used in the current systematic reviews

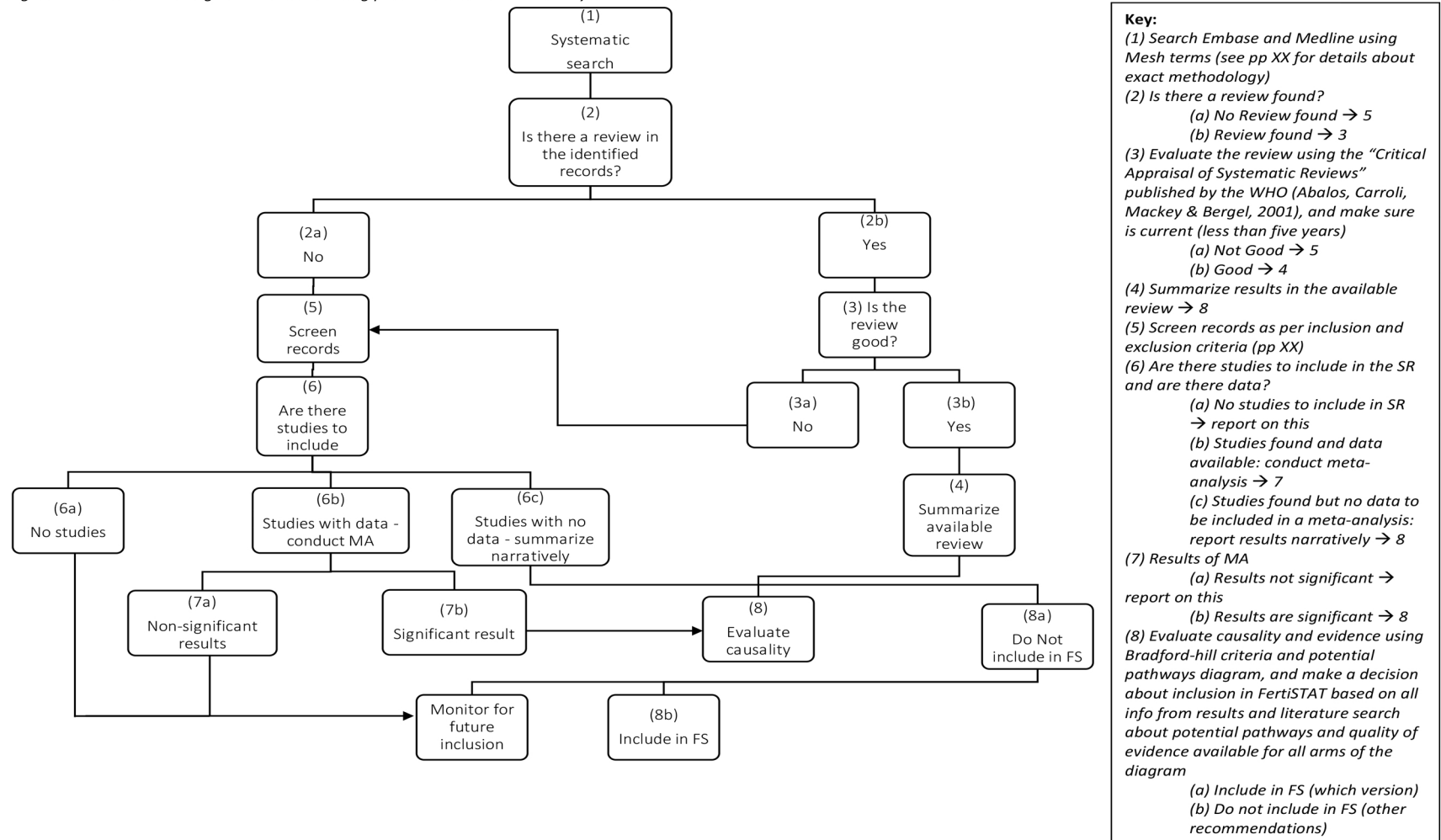


Figure 3.2. Flowchart showing the decision making process used in the current systematic reviews. MA = meta-analysis; FS = FertiSTAT

the primary studies identified in the search were subjected to screening, assessing eligibility using inclusion and exclusion criteria, quality evaluation, meta-analysis (where relevant) and reporting. If the eligible primary studies contained relevant data a meta-analysis was conducted otherwise the results were summarised narratively. For all RFs, results of the systematic review were aggregated with extant literature to develop pathway diagrams that could aid in the decision about inclusion in FertiSTAT and gaps in knowledge that need to be addressed in future research. The specific steps in the review procedure are shown below.

Search Strategy

Ovid Medline was searched from 1946 to April 2015. Fertility problems were searched and combined with 'OR' using the following MeSH terms: 'female fertility', 'female infertility', 'fertility' and 'infertility'. All terms related to the potential RF (e.g. consanguinity) were searched and combined with 'OR'. Search terms for the RF were combined with search terms for fertility problems using 'AND' (see Appendix E for the order of steps and MeSH terms used). No limits on language or date were used in the search. The same search strategy was used to search Embase 1947 to July 2015, the Cochrane library and other databases that might be relevant to low resource settings including LILACS, INDMED, Africana Periodical Literature and African Index Medicus. Key organisational websites were searched using the same search terms, including the WHO, United Nations Population Fund (UNFPA), as well as regional sites of these organizations such as the Eastern Mediterranean Regional Office (EMRO) and African Regional Office (AFRO) of the WHO.

For all reviews the primary outcome used was 'fertility problems'. The same search terms (fertility and infertility) as those used in the development of the FertiSTAT (Bunting & Boivin, 2010) were used in the current review. All outcomes yielded from these search terms (e.g. time to pregnancy, medical diagnosis of infertility) including outcomes of gestational

problems and childlessness, were included. The gestational problems and childlessness outcomes were used to enable an examination of the impact of the RF on ability to become pregnant separately from the ability to have a live birth.

The exclusion criteria were: (1) use of non-human animal data only, (2) use of male data only, (3) fertility related outcome not reported, (4) association between the RF and fertility outcome not reported, (5) the RF reported not of interest, (6) time to birth/duration of childlessness was (on average) less than 21 months because that would imply that pregnancy had occurred within the presumed fertile period of 12 months (i.e., 12 months trying plus 9 months gestation) and (7) study used secondary or qualitative data or was a publication or duplicate record of an included study (see Appendix F for full list of exclusion criteria).

A search of the reference lists of the included articles was conducted to identify new studies and authors were contacted for missing information. All searches were updated in December 2016 to ensure newer studies were included. To ensure the comprehensiveness of the original search terms we had to determine if we had missed relevant studies that measured the RF and specific fertility problems without mentioning the word fertility and infertility. Therefore, we tested the robustness of our decision by replicating the searches combined with MeSH terms for specific fertility problems (e.g., tubal occlusion, amenorrhea, time to first birth) that did not include the words fertility and infertility, see Appendix G for list of updated MeSH terms. Results reported in each review pertain to original and updated searches (number reported separately in review flow charts).

Assessment of Bias

The term bias is defined as divergence of results or inferences from the truth, or any process leading to such a change (Grimes & Schulz, 2002). There are various types of bias that can affect the internal validity of meta-analyses: selection bias, information bias, recall

bias, and bias due to confounder. In the present study the different types of bias were assessed using the modified version of the Newcastle-Ottawa Scale [NOS] (Wells, et al., 2010).

Selection bias occurs when the exposed and non-exposed group differ on important aspects other than the exposure, which can cause misleading results (Grimes & Schulz, 2002). Information bias occurs when data is collected in a different manner from the exposed and non-exposed groups (Grimes & Schulz, 2002). Recall bias arises when there is differential reporting of information (intentional or unintentional) about the exposure or outcome by subjects in one group compared to the other group (Sackett, 1979). This can lead to misclassification of the subjects according to the exposure or outcome (Grimes & Schulz, 2002) and can be a risk to the internal validity of the study (Hassan, 2005). Recall bias is greater in situations where the disease or event being studied is critical or significant e.g. cancer, congenital malformations; if a specific exposure is perceived as a RF for the disease or if a scientifically ill-established association has been publicised by the media (Margetts, Vorster & Venter, 2003; Wynder, 1994; Raloff, 1998). Bias due to confounder occurs when confounders are not taken into account either through study design or in the statistical analysis. A confounder is a variable that is associated with the exposure and has an impact on the outcome, but is not an intermediate link between the two (Grimes & Schulz, 2002). Researchers should identify all possible variables that can indirectly affect the association under study, and develop a suitable design that can incorporate the effect of these variables. This can be done through matching of exposed and non-exposed group subjects, by including these confounders in a multivariate analysis of the data or by stratification, i.e. the grouping of results by levels of the confounder (Grimes & Schulz, 2002).

Data Extraction and Quality Assessment

A standard form was developed and used for extraction of data from included studies. The author and her supervisor pilot tested several iterations of the standard form, see Appendix H. The author and research assistant (Kawther Mohamed, KM) extracted the information. Information was extracted on study design (case-controlled, cross-sectional), sample (location, size), definition of RF (type of relative, coefficient of inbreeding), the primary outcome fertility problems (as indicated by different outcomes available for each RF), confounders and data relevant to effect size calculation. Quality assessment of the included studies was based on an adapted version of the NOS and included six criteria. First, RF was adequately assessed when there was independent validation (e.g. more than one person/record/time/process, or reference to primary record source such as medical/hospital records) (1 point) and if the RF was representative of the cohort i.e. drawn from the same population (1 point). Second, controls (non-exposed) were considered to be adequately assessed when selection was comparable to cases, and RF was excluded properly in the control population (up to 2 points). Third, comparability of controls was achieved if exposed/non-exposed were matched or adjustment for confounds made during analysis. One point was awarded for control of (the most relevant confounder for that RF) or for any other confounder (e.g. education) for a maximum of 2 points. Fourth, confounders were considered adequately assessed if data were obtained from records or a blind interview (1 point), and when the same method was used for both case and control groups (1 point) (maximum 2 points). Fifth, fertility problems outcome was adequately assessed if independent or blind assessment was stated in the study, or confirmation of the outcome by reference to secure records (e.g. medical records) (up to 1 point). Sixth, one point was given if attrition was less than 20% for both groups (this is only applicable to longitudinal studies). The overall quality rating was low (0 to 3 points), average (4 to 6 points), or high (7 to 10 points).

Publication Bias

Bias that can affect the generalizability of the results of the review such as publication bias, was also examined. Publication bias refers to the situation where research findings are *published* or *not-published*, contingent on the nature and direction of the results (Higgins & Green, 2011, Chapter 10). Although the selective recommendation by peer reviewers has been suggested as a source of publication bias, it appears that the selective submission of papers by authors may be the prevailing contributor. One method suggested to avoid this bias is the inclusion of grey literature (Higgins & Green, 2011, Chapter 10). Publication bias can be investigated using various techniques including funnel plots. It has been suggested in the literature that 10 or more studies are required to enable visual assessment of the funnel plot (Mavridis & Salanti, 2014). With fewer studies the test would have very little power to distinguish real funnel plot asymmetry from chance (Higgins & Green, 2011, Chapter 10). Funnel plots can be supplemented with other tests of publication bias such as Eggers test and trim and fill procedures. Egger's test is used to identify if there is evidence of any bias, whereas trim and fill is used to assess the impact of the bias (Borenstein, Hedges, Higgins & Rothstein, 2009, Chapter 30). Egger's test calculates the slope of the regression (bias coefficient) which is used to specify the degree of bias. Trim and fill method is an iterative non-parametric procedure used to impute the number of "missing" studies in the meta-analysis, and to calculate the adjusted pooled effect estimate with the "missing" studies. However, the trim and fill procedure assumes that publication bias is the only source of funnel plot asymmetry, which is an unrealistic assumption (Mavridis & Salanti, 2014). These methods do not guarantee the validity of the results of the meta-analysis (Sutton, Song, Gilbody & Abrams, 2000; Kicinski, 2014), but they allow an identification of a potential shortcoming of the review. All these methods were used in the present study to ascertain the presence and impact of publication bias on the results of the current meta-analyses.

Data Synthesis and Analysis

Review Manager (RevMan) [Computer program]. Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), was used to calculate effect sizes and meta-analysis and to generate forest plots. The primary outcome measure of association between an exposure and an outcome used was the odds ratio (OR). ORs were calculated from raw data presented in the primary studies as number of events and totals (Kirkwood & Sterne, 2003, Chapter 16, pp159-160, see Appendix I for calculations).

In all included analyses an OR of one implied no difference between the exposed (RF) and non-exposed (no-RF) groups, an OR greater than one indicated that the exposed group were more likely to have fertility problems (as indicated by the outcomes available in each search) than the non-exposed group, and an OR less than one indicated that the exposed group were less likely to have fertility problems than the non-exposed group.

When means and standard deviations were presented in the primary studies, the primary outcome measure was the mean difference (MD) between exposed and non-exposed groups and original units of measurement were used. Meta-analyses were computed separately for the different outcomes of fertility problems that were reported in the primary studies in each review.

Given that multiple mechanisms may influence how the RFs affect fertility there may not be one true effect size, therefore a random effects model was deemed appropriate for the data analysis. Heterogeneity was tested using the Q statistic and I^2 index, which specifies the proportion of variance in the effect size not due to chance. Where heterogeneity was statistically significant, subgroup/sensitivity analysis were conducted. The subgroup analyses were based on differences in methodological characteristics of the study e.g. type of control group, subcategories of infertility (tubal factor vs ovulatory). Funnel plots, Egger's test and trim and fill procedures were used to evaluate publication bias using Comprehensive Meta-

Analysis software (Comprehensive Meta-Analysis (Version 2) [Computer software]. (2014). A probability level of $P < 0.05$ was used to determine the significance of change in the pooled effect size. Where there were only two studies in an analysis publication bias could not be assessed using funnel plots or trim and fill. Any alterations to this general method were reported in the individual reviews' method section.

When data in primary studies were not sufficient to calculate pooled estimates in meta-analyses a narrative review of the systematic evidence was conducted. In such cases the available evidence from the search and from known sources was summarized and conclusions on the potential impact of the RF on fertility were reported.

Study 3.1: Systematic Review and Meta-analysis of observational studies examining the association of consanguinity and fertility problems

Introduction

Consanguinity was one of the risk factors identified through the process of adapting the FertiSTAT and was endorsed by the experts in Study 2.1 (Chapter 2, pp. 25). The validity of this risk factor as a predictor of fertility problems was examined in the current systematic review using the operational definitions of fertility problems and risk factor applied in the original development of FertiSTAT (Bunting & Boivin, 2010).

Description of consanguinity

A consanguineous (CSG) marriage is one that is contracted between close biological relatives (Bittles, 2001). Consanguinity (CSG) can be measured using a coefficient of inbreeding, which expresses the degree of relatedness of the couple as a percentage of shared genetic makeup between the two individuals. Figure 3.1.1 is an illustration of degree of relatedness among different family members. As shown in Figure 3.1.1 a person married to their first cousin would have 12.5% shared genetic material. Marriages further than second cousins (i.e., coefficient of inbreeding equal to or less than 0.0156) are not considered CSG as the shared genetic material in these marriages is similar to that in the general population. The worldwide prevalence of CSG marriages is divided into areas of low (less than 1%), medium (1-10%) and high (20-50%) percentage of marriages (Bittles, 2001; Bittles, 2014). Figure 3.1.2 shows that America, Europe and Australasia are in the low group, Japan and South America in the medium group and North Africa, West, Central and South Asia in the high group. Sudan has one of the highest prevalence of CSG in the world, with more than 50% of marriages being CSG, second only to Pakistan (Bittles, 2014). Some religions like Judaism, Buddhism and Islam allow CSG marriages whereas other religions such as

Christianity and Hinduism prohibit first-degree cousin marriage (Bittles, 2001). In many countries including China and some American states, there are civil laws prohibiting CSG marriages. First-degree cousin marriage is not prohibited in the Quran, and is considered as *Sunna* meaning that it is ‘favoured’ (Bittles, 2001). These religious and legal differences between countries can help explain international differences in rate of CSG shown in Figure 3.1.2. There is a distinction between CSG and endogamy. The former is marriage between biological relatives whereas the latter is marriage between members of a; tribe, ethnic group or clan

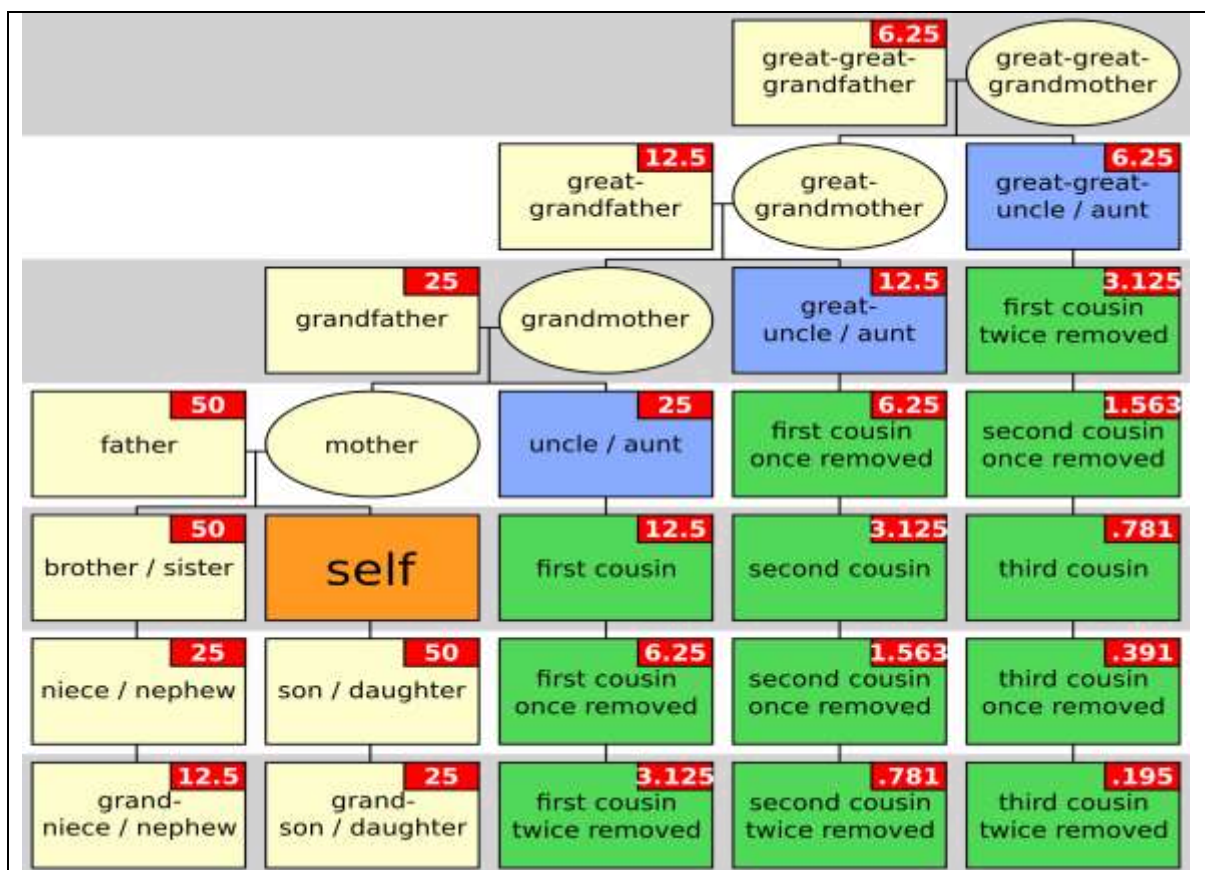
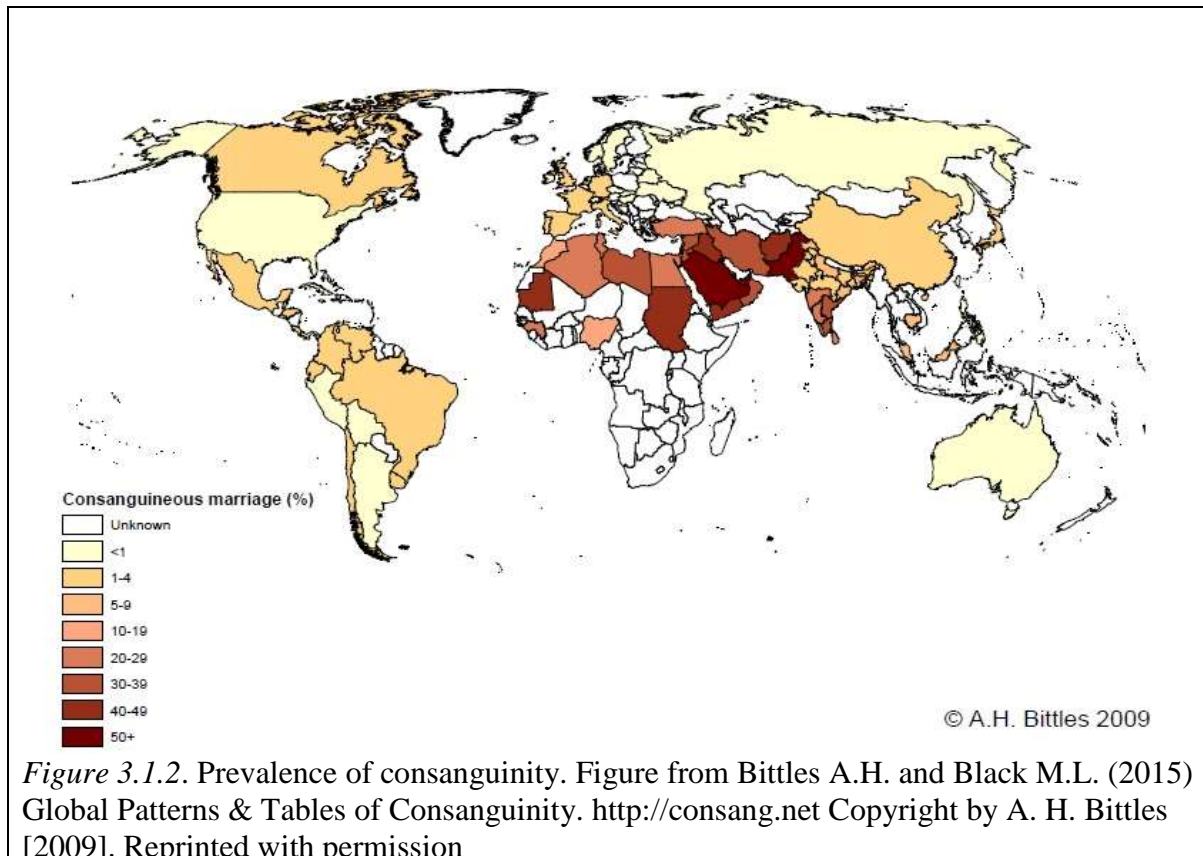


Figure 3.1.1. Degree of relatedness in CSG relative to the self. Numbers in the red box represent the degree of relatedness as a percentage of shared genetic makeup to self. Blue shading is uncle/aunt, Green shading is cousin. Yellow shading is parents, siblings, grandparents, grandchildren, nieces and nephews. Figure from <http://greatoaksgrow.blogspot.com/> Copyright by Judi Heit. Reprinted with permission



(Bittles & Black, 2010). In endogamy the genes from a common ancestor will pool more gradually than in a CSG marriage, thus the effect of the shared genes will take longer to become manifest. Additionally, a study of endogamous groups would theoretically show the impact of inbreeding due to the couple only as well as due to the several in bred generations i.e. effect of inbred parents on their reproductive abilities and progeny. Thus, a study examining the effect of CSG on individual infertility should be limited to the effects of marriages between relatives rather than focusing on populations with high rates of endogamy, to enable inferences on the direct impact of couple genetic similarity on individual fertility.

Plausible Mechanisms to Explain why CSG Could be Associated with Fertility Problems

Numerous causal mechanisms linking CSG and fertility have been proposed to explain the heterogeneity in study results, see Figure 3.1.3. The arguments proposing that

CSG could indirectly have a positive effect on fertility, have suggested the following mechanism as an explanation; younger age at marriage, longer reproductive span, reproductive compensation and gamete compatibility. Cultures that encourage CSG marriages also encourage a younger age at marriage, and thus younger age could be a moderator of the effect of CSG on fertility. In cultures where CGS marriages are most common, the average age of marriage for women tends to be much younger (e.g. 17.8 in India, for 2006) than where CSG is relatively rare, for example in western countries [e.g. 29.9 in the UK for 2009] (UN, Department of Economic and Social Affairs, Population Division, 2013). Age and age at marriage can impact on other risk factors that could then potentially have a cumulative effect, as in the case of the multiplicative relationship between age and time trying (Bunting & Boivin, 2010). Younger age may lead to higher pregnancy rate because of age per se, or because the longer reproductive span would allow reproductive compensation over time. Reproductive span refers to the period during which the individual is biologically fertile and thus able to reproduce (International Institute for population Sciences, 2000). Reproductive compensation refers to the eventual replacement of lost infants or foetuses with surviving infants through subsequent reproductive effort (Reed, 1971). Age, a longer reproductive span and reproductive compensation have been examined in studies assessing the impact of CSG on pregnancy, abortion, stillbirth and live birth rate.

It has also been proposed that CSG has a negative impact on fertility. One argument is that the concentration of recessive genes leads to increased morbidity and mortality in the offspring of CSG couples due to increased homozygosity and the genetic abnormalities it produces (Bittles & Black, 2010). Recessive genes are those that are only expressed in the offspring if inherited from both parents, and increased homozygosity refers to offspring that have inherited the same gene from both parents regardless of whether the gene is recessive or not (Hamamy, 2012).

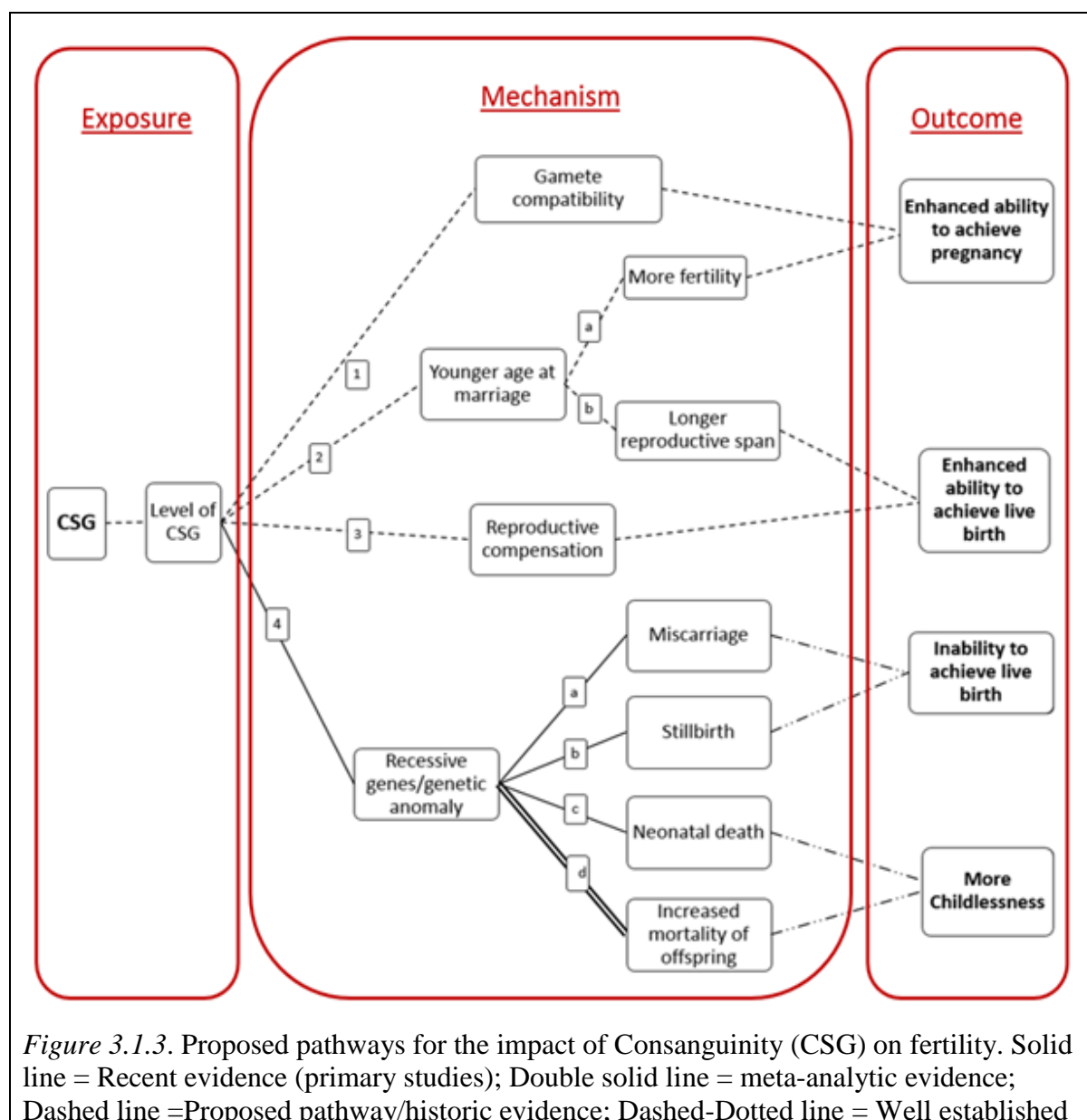


Figure 3.1.3. Proposed pathways for the impact of Consanguinity (CSG) on fertility. Solid line = Recent evidence (primary studies); Double solid line = meta-analytic evidence; Dashed line = Proposed pathway/historic evidence; Dashed-Dotted line = Well established

Reproductive Health Consequences of CSG

Extant research is mixed about whether CSG is a risk factor for fertility problems, with some studies reporting a negative impact, while others report a positive impact. Table 3.1.1 condenses results of five reviews summarized below. The reviews summarized were subjected to quality evaluation using the “Critical Appraisal of Systematic Reviews” published by the WHO (Abalos, Carroli, Mackey & Bergel, 2001).

Table 3.1.1.

Summary of reproductive health consequences of CSG reported in the literature

Reproductive outcome	Effect of CSG	Statistics reported (where available)	Review
Positive effect			
Live birth rate	Statistically significant in the first cousin only but not in other categories of CSG	First cousins had 0.26 more children	Bittles et al., 2002
	Higher live birth rate in first cousin marriages compared to non-CSG marriages	Mean live births range in first cousins (2.26-7.48) in non-CSG (2.14-5.83)	Hussain and Bittles, 2004
Negative effect			
Mortality of offspring	More mortality in progeny of first cousins compared to non-CSG progeny	Meta-analysis showed significant mean excess mortality of 3.5% in the CSG progeny ($r^2 = 0.70$; $P < 0.00001$)	Bittles & Black, 2010
Mortality and morbidity of offspring	Higher rates of infant morbidity and mortality in offspring of CSG couples than non-CSG couples where reported	Range of infant morbidity 1.34-42% in CSG and 0.81-25% in non-CSG, mortality 0.95-8.6% in the CSG and 0.63-5.3% in non-CSG	Bhasin & Shampa, 2012
Recessive genes in offspring	Probability of inheriting recessive gene increases with the increase in the proximity of the relationship between parents	NR	Hamamy, 2012

Note. NR = not reported; CSG = consanguinity/consanguineous

In a systematic review of the CSG literature, Bittles, Grant, Sullivan, and Hussain (2002) included data from 30 populations in six countries, and investigated the number of live births in four CSG categories (second cousin, uncle-niece, first cousin and double first cousin) versus non-CSG groups. A positive association between CSG and live births at all levels of CSG was reported, reaching statistical significance at first cousin level, indicating that first cousins had on average 0.26 more live births than non-CSG couples. In addition to the systematic review, multivariate analysis was also computed on data from the National Family and Health Survey conducted in India (1992-1993) to examine the effect of socioeconomic variables. The results of the multivariate analysis revealed no significant

association between CSG and live births when variables predictive of high fertility (i.e., duration of marriage, reproductive compensation, illiteracy, earlier age at marriage and lower contraceptive uptake) were included in the analysis. From these data, Bittles et al. (2002) concluded that the two most important variables to explain higher live births in consanguineous marriages were a longer reproductive span and reproductive compensation. Other proposals have been made for a beneficial effect of CSG on live births. For example, that the similarity and presumed compatibility of the uniting gametes (maternal and paternal) due to shared genes is beneficial (Shami, Schmitt, & Bittles, 1990; Hann, 1984; Bittles, Mason, Grenne & Rao, 1991) but no evidence has been given to support this hypothesis.

In a narrative review Hussain and Bittles (2004) reported results of the effects of CSG on live birth rate, from a literature review of CSG studies and Demographic and Health Survey (DHS) data from Pakistan and India. The authors used the comprehensive database on consanguineous marriage which was developed by Bittles and is reported to be the most comprehensive database of all published and unpublished studies on CSG. Additionally, data from the DHS were used to estimate live birth rate in CSG and non-CSG marriages. Although the methodology of the review was adequate pooled estimates were not reported. Results from the literature review showed a higher live birth rate in first cousin marriages compared to non-CSG marriages, however, this finding was not supported using DHS data. Specifically, data from Pakistan showed lower live birth in CSG versus non-CSG marriages, and data from India showed similar rates between CSG and non-CSG groups. Paradoxically, the multivariate analysis in India and Pakistan showed that CSG was associated with lower maternal education, younger maternal age at marriage, less contraceptive use, and rural residence; all factors associated with higher live birth. The proposed explanation for this paradoxical result was that there could be misclassification of degree of CSG in the Pakistani DHS data. The participants may have misclassified themselves as closer relatives (first

cousins) when the relationship was in fact further apart, which is likely because of the highly endogamous nature of the Pakistani society (Hussain & Bittles, 2004). This misclassification would then inflate the degree of non-genuine consanguinity, which in turn would dilute the effect of CSG marriages, hence underestimating the effect.

In a review on the impact of CSG on fertility, Bittles and Black (2010) conducted a meta-analysis examining case-controlled studies comparing progeny of first cousins with non-CSG progeny in 69 populations (15 countries) with a total sample size of 2.14 million. Although the review was very comprehensive and meta-analysis was conducted search methodology was not reported and could thus not be gauged or replicated. The results revealed a significant mean excess mortality of 3.5% in the CSG progeny versus non-CSG group. The difference was attributed to biological factors (i.e. homozygosity of recessive genes) as well as contextual factors, such as marital violence and family income.

In a recent review of studies in India examining the relationship between CSG and fertility, 78 studies from India were examined with regards to increased morbidity and mortality in the offspring of CSG versus non-CSG couples (Bhasin and Shampa, 2012). The authors present data mainly on India and a brief summary of studies published elsewhere, however, search methodology was not presented, limiting an evaluation of the quality of methods. Higher rates of infant morbidity and mortality in offspring of CSG couples than non-CSG couples were reported, but a meta-analysis was not conducted, therefore no overall pooled effect size were available. The range of infant morbidity reported was 1.34-42% in the CSG and 0.81-25% in the non-CSG groups, while mortality was 0.95-8.6% in the CSG and 0.63-5.3% in the non-CSG groups, results varied by disease and region included in the reviewed studies. According to Hamamy (2012) a possible explanation of this higher rate is that the common genetic material increases the likelihood of recessive genes being pooled i.e. increased homozygosity for harmful genetic conditions.

In a narrative review of the literature on social and biological aspects of consanguinity, Hamamy (2012), reported on studies that indicate an increased expression of autosomal recessive disorders due to mutations inherited from a common ancestor. Although this review was comprehensive in its coverage of topics and number of studies cited, search methodology was not reported, limiting evaluation of the review and replicability. The results showed that the probability of inheriting identical copies of the recessive gene increases with the increase in the proximity of the relationship between the parents. However, specific rates or overall effects were not reported because this was a narrative review. Thus offspring of CSG couples are more likely to have expression of harmful autosomal recessive disorders. Although these disorders can result in increased loss of fetuses and infant mortality they would not impact the ability to achieve pregnancy. As such they might need to be included in the FertiSTAT

In addition to the reviews discussed thus far, another argument supporting the negative impact of CSG comes from studies of the Hutterites, a group of 30,000 people that descended from 100 ancestors, with a very high rate of inbreeding (Martin, 1979). The suggested mechanism is that couples' that share human leukocyte antigens (HLAs) will take longer to become pregnant (Ober, Elias, Kostyu & Hauck, 1992; Ober, Hyslop, & Hauck, 1999). HLAs (also known as major histocompatibility complex [MHC]) are a group of genes that are part of the immune system (Janeway, Travers, Walport & Shlomchik, 2001). The HLAs help the immune system to differentiate self-cells from non-self-cells (foreign cell). A cell that has the person's HLA will be recognised as a self-cell, whereas a cell not displaying the person's HLA will be identified as foreign and the immune system will respond accordingly. Some HLAs are involved with foreign proteins *inside* the cell (HLA-A, B and C) and others are involved with foreign proteins *outside* the cell (HLA-DP, DM, DOA, DOB, DQ, and DR). HLA compatibility refers to similarity of antigens, for example between donor

and recipient in a transplant or between the foetus and mother in pregnancy (Bolis, Soro, Martinetti Bianchi, & Blevedere, 1985). A CSG couple share more HLAs than a non-CSG couple and the closer the level of CSG the more HLAs will be common. Consequently, HLA compatibility between foetus and mother will increase with level of CSG because the HLAs inherited from the father will be similar to those of the mother. Ober et al. (1992) studied the effect of HLA on pregnancy in 104 couples among the Hutterites of the United States. The average degree of relatedness in the sample was slightly greater than that of first cousins once removed (coefficient of inbreeding $F=0.0368$). HLAs were determined by genetic testing of blood samples from all participants in the study. A significantly longer time to clinical pregnancy was observed in the Hutterite group that had shared antigens at a specific type of locus (HLA-DR) than in the group that did not have shared antigens at that locus. Specifically, the group with shared HLA-DR took 5.1 months to become pregnant whereas the group with no shared HLA-DR took 2 months.

The effect of inbreeding on time to pregnancy was re-examined in the Hutterites in a later study (Ober et al., 1999). In this study a sample of 132 women was sampled from a subgroup of the Hutterites known as the S-leut (average coefficient of inbreeding $F=0.032$). Results indicated that the time to pregnancy was significantly longer in women with F greater than 0.04 (6 months), compared with women with F less than 0.04 (less than 5 months). As the difference in foetal loss was not significant, it suggested that the longer time to pregnancy was likely due to delay in conceiving rather than delay due to repeated miscarriage. It is important to note that in both Ober et al. (1992) and Ober et al. (1999), inbreeding was studied at a population level, which means that inferences may not be applicable at the individual couple level. Since couples in endogamous populations are themselves descended from parents and grandparents that are genetically similar it is difficult to determine if the effect on fertility is that of the parent being a progeny of relatives or the effect of the couple

being related. The findings on time to pregnancy in the Hutterites will therefore not be used to support the current review, rather they are provided to elucidate potential mechanism of action that could provide a plausible explanation for the impact of shared genes on fertility problems.

The mixed results in extant literature may be due to methodological difference in: outcomes (pregnancy, live birth); exposure duration and time frames (12, 24 months, 5 years, current, life time), and; sample (population or individual). Heterogeneity in design makes it difficult to ascertain whether CSG impacts on ability to get pregnant, to maintain a pregnancy, or morbidity and mortality of the offspring. Hypotheses about which aspects of the reproductive process are affected have been proposed, however, a lack of rigour and consistency in reporting on search methodology in the available reviews limits their utility and necessitates a systematic review with rigorous methodology and transparency.

Rational, Aim and Objectives

The results of the studies reviewed thus far indicated that CSG (shared genetic material) may compromise fertility at multiple points in the reproductive process, including a longer time to pregnancy (conception), a lower or higher number of live births (gestation), and higher infant mortality and morbidity (postnatal). The biological plausibility of CSG effects on the reproductive process coupled with the high prevalence of CSG in some developing countries and the results of the survey of physicians [CSG endorsed as a potential risk factor by 50% of responders] (Chapter 2, pp. 25), highlights the need to investigate whether CSG should be included as a risk factor in the adapted FertiSTAT. The present study reports on results of a systematic review and meta-analyses of studies on consanguinity. The objective of the review was to examine whether CSG was associated with fertility problems in women, and at what point in the reproductive process CSG might exert its effects. The

population of interest for the reviews was women, the exposure was CSG at the individual level and the outcome of interest was fertility problems. In the current study analyses were separated by outcome (pregnancy and childlessness) as well as duration (time to first birth, 10/20 or more years of marriage and lifetime) to identify whether the effect of CSG was on ability to become pregnant or post-implantation (gestation, perinatal) and how long CSG exerts its effect. The overall aim of this review was to determine whether CSG should be included as a risk factor in the adapted FertiSTAT.

Materials and Methods

Search Strategy

The search terms included words related to consanguinity, for a complete list of MeSH terms see Appendix J. Studies were excluded if level of CSG was at group level (i.e. kinship and endogamy), because only the effects of CSG on the individual was of interest, therefore endogamy or kinship was not included.

Data Extraction and Quality Assessment

The data extraction form (Appendix H) was adapted to include information relevant to CSG. The NOS form was adapted to reflect quality criteria for the assessment of CSG and additional confounders. GTB was adequately assessed if independent validation of the degree of relatedness was assessed (e.g. more than one person/record/time/process, or reference to primary record source such as medical/hospital records) or coefficient of CSG was calculated. The most relevant confounder was 'age at marriage'.

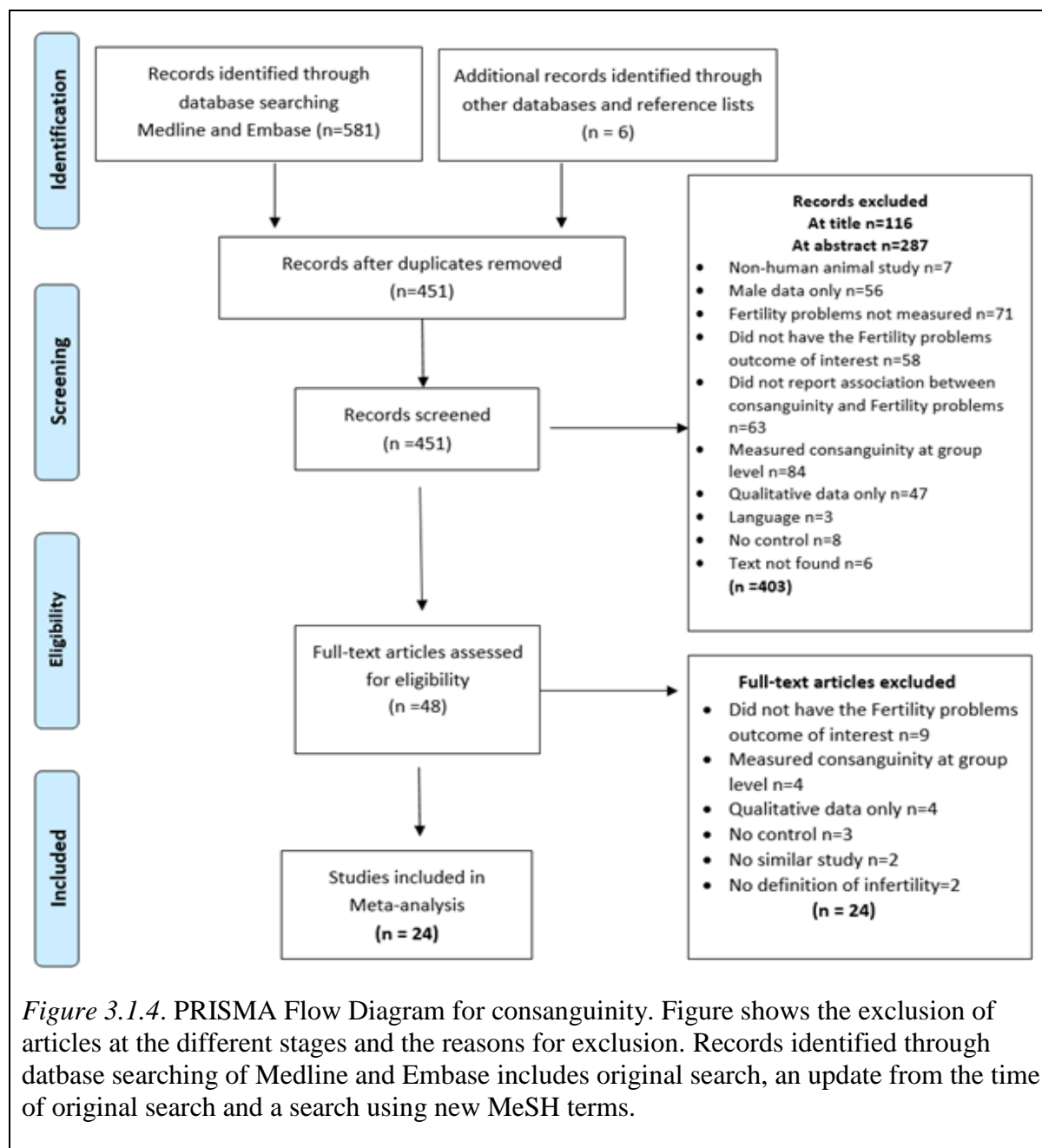
Data synthesis and analysis

Meta-analyses were computed for the outcomes reported in the studies and subgroup/sensitivity analyses were planned according to methodological characteristics of the study, including duration of outcome measure. One study reported on several groups with varying durations of marriage (Rao, 1979). The results from the different subgroups within this study were treated as different studies in the analyses, because the groups were independent.

Results

Study selection

Figure 3.1.4 shows the flowchart for number, reason and stage of exclusion of articles. A total of 451 records were identified (after duplicates removed) and most studies (274 of 451, 60.8%) were excluded because they included male data only, did not include the outcome of interest, reported no association between fertility problems and CSG or reported CSG at group level only. For three of nine non-English studies (two in Japanese and one in Russian) translations were not available at the time of analysis, and these studies could not be included. Six studies used the terms ‘infertility’ or ‘sterility’, without an operational definition. The authors were contacted to provide the definition of ‘infertility’ and duration of infertility to inform decision about inclusion. Three authors replied and the studies (Guz, 1989; Zlotogora, 1997; Fuster, 2003) were excluded because they did not meet inclusion criteria. One author did not reply and the study was excluded (Freire-Maia, 1975). Search of the reference lists of the included studies and contact with authors resulted in no additional studies. One study (Haq, 2008) reported on women diagnosed with PCOS and infertility in CGS versus non-CSG marriages, however, no other study reported similar outcome to compare it with. Of the 48 full text articles assessed for inclusion, 24 met inclusion criteria and were included in meta-analyses.



The searches using the updated MeSH terms (see Chapter 3 General Methods, pp 60) indicated that all relevant studies had been captured using the words fertility and infertility, and the additional studies captured were not relevant according to our inclusion/exclusion criteria (e.g., on fertility in non-human animals). This was the case for all RFs reviewed.

Characteristics and Design of Included Studies

Table 3.1.2 shows selected sample characteristics of the included studies. The majority (20 of 24, 83.3%) of studies were carried out in Asia and the Middle East and four (16.7%) were conducted in Europe. Only six of the 24 (25%) studies included information related to participant age at marriage. The average age (years) at marriage in CSG women was 23.1 (6 studies), in non-CSG women was 23.6 (5 studies), in CSG men was 26.3 (4 studies) and in non-CSG men was 27.9. Table 3.1.3 shows methodological characteristics of included studies. The design of 20 studies was cross-sectional and four studies were cohort (three retrospective and one prospective). The majority obtained data through household interview. CSG was reported as type of relationship between spouses (e.g., cousin, uncle) in all studies. The following outcomes were reported in the included studies: (1) three reported ‘never-pregnant’, (2) five reported ‘childless’, (3) seven reported ‘miscarriages’, (4) seven reported ‘stillbirths’, (5) seven reported ‘neonatal death’, (6) two reported mean ‘time to pregnancy’ in years, (7) five reported mean number of ‘pregnancies’, and (8) seven reported mean number of ‘live births’.

Study Quality, Fertility Problems Outcome Measure and Bias

Table 3.1.4 shows the results of quality assessment (see table footnote for criteria). CSG was adequately assessed and representative of the population in 13 of the 24 studies (54.2%). The non-CSG group were selected from the same populations and exclusions were adequately reported in 21 of 24 studies (87.5%). Comparability of at least one confounder was reported in 17 of 24 studies (70.8%). Half the studies used only self-report to assess

Table 3.1.2.

Sample characteristics of the 24 included Studies

Study	Location	Sample (n)	CSG (n)	Non- CSG (n)	Mean age at marriage			
					Women		Men	
					CSG	Non-CSG	CSG	Non-CSG
Edo, 1985	Spain	965 couples	272	693	25.74	26.02	28.9	29.2
Hann, 1984	Karnataka State in South India	1885 women	722	1163	NR			
Tanaka, 1977	Fukuoka, Japan	1450 couples	346	1104	NR			
Yamaguchi, 1975	Fukuoka, Japan	4026 couples	2173	1853	NR			
Bittles, 1993	Punjabi Provence of Pakistan	9520 women	4784	4736	18.97	19.74	23.81	25.97
Rao, 1979	Southern India District of Tamil Nadu	15, 926 women	6379	9547	NR			
Shami, 1990	Punjabi Provence of Pakistan	3329 women	2227	1102	18.95	19.93	23.7	26
Al-Kandari 2007	Kuwait	7315 women	4009	3306	NR			
Bener 2006	Qatar	1515 women	818	687	NR			
Blanco 2006	Leon, Spain	2670 women	474	2196	25.63	26.70	28.81	30.39
Ciceklioglu 2013	Bayrakli, suburb of Izmir, Turkey	170 women	85	85	NR			
Devi 1981	Karnataka, South India	3254 women	920	2301	NR			

Study	Location	Sample (n)	CSG (n)	Non- CSG (n)	Mean age at marriage			
					Women		Men	
					CSG	Non-CSG	CSG	Non-CSG
Fuster 2003	Los Nogales, Galicia, Spain	1581	132	1449	24.58			
Khlat 1988	Beirut, Lebanon	2801	705	2096	NR			
Khoury 2000	Jordan	1867	947	920	24.6	25.8		
Luna 1990	La Alpujarra, Andalusia, Spain	647	75	572	NR			
Abdulrazzaq 1997	Alain & Dubai, UAE	2033	1026	100	NR			
Al Husain 1996	Riyadh, KSA	2001 couples	1022	979	NR			
Asha 1981	South India	377 women	156	211	NR			
Gharyeb 2014	Yatta, Palestine	500 women	305	195	NR			
Islam 2013	Oman	2037 women	1052	985	NR			
Saha 1990	Khartoum, Sudan	926 women	586	340	NR			
Verma 1992	Pondicherry, India	1000 women	308	692	NR			
Yuksel 2009	Malatya, Turkey	409 women	116	293	NR			

Note: CSG = consanguineous/consanguinity; ^aMean age for women at the beginning of the study; NR= data not reported

Table 3.1.3.

Characteristics of the design of the 24 included studies

Study	Study design	Data collection	Study period	CSG measure	Fertility Problems outcome measure (duration)
Edo, 1985	Retrospective cohort	Extracted from parish records and civil registries	1900-1974	1 st and 2 nd degree cousins	Childless marriages at the end of reproductive life (age 45)
Hann, 1984	Cross-sectional	Household interviews	Not reported	1 st degree cousin and Uncle-niece	Primary sterility defined as never having conceived in (1) women who have completed reproduction (over 40, menopausal or widowed) or (2) after 10 years without contraception in women of reproductive age
Tanaka, 1977	Retrospective cohort	Household interviews in 2 rural villages and cross-checked with records	Not reported	CSG between spouse, between husband's parents and between wife's parents	Infertility defined as never been pregnant after living with husband for more than 5 years
Yamaguchi, 1975	Retrospective cohort	Household interviews in rural villages and cross-checked with records	Not reported	CSG between spouse, between husband's parents and between wife's parents	Sterility defined as no pregnancy after more than 5 years of marriage
Bittles, 1993 (not in 71)	Cross-sectional	Household & hospital interviews in 11 cities	1979-1985	Mixed, double 1 st cousin, 1 st cousin, double second cousin, second cousin,	Time to first delivery from start of marriage in years
Rao, 1979	Cross-sectional	Household interviews in In 14 rural and urban districts	1969-1975	Mixed, uncle-niece, first cousin, beyond first cousin	Primary sterility defined as a married woman who has not had a live-born baby after consummation of marriage and unprotected sexual activity (duration in 5 year intervals)
Shami, 1990	Cross-sectional	from general hospital and labour wards, as well as door-to-door interviews	1980-1983	Mixed, double first cousin, first cousin, first cousin once removed, second Cousin.	Time to first birth from start of marriage in years
Al-Kandari 2007	Cross-sectional	Questionnaires filled by women attending 10 different PHC	2002	Double cousin, first cousin, second cousin, third cousin	Number of births per women

Study	Study design	Data collection	Study period	CSG measure	Fertility Problems outcome measure (duration)
Bener 2006	Cross-sectional	Questionnaires filled by face-to-face interviews from 10 health centres mostly visited and women's hospital	2004	Double cousin, first cousin, first cousin once removed, second cousin, less than second cousin	Number of pregnancies and live births
Blanco 2006	Cross-sectional	La Cabrera parish registers	1880-1959	Up to third degree	Live births
Ciceklioglu 2013	Cross-sectional	Community based in-person interviews from 3 neighbourhoods in Bayraklu	2009	First and second degree cousins	Number of pregnancies and deliveries
Devi 1981	Cross-sectional	17 hospitals, maternity homes and health centres from records or interviews by staff	1971	Beyond second cousin, second cousin, first cousin, uncle-niece	Mean number of live born
Fuster 2003	Cross-sectional	Biodemographic data from parish and Lugo bisphoric records	1871-1977	Uncle-niece, first cousin, first cousin once removed, second cousin, second cousin once removed, third cousin	Mean birth
Khlat 1988	Cross-sectional	2752 household were interviewed	1983-1984	First cousin and more distant than first cousin	Mean number of pregnancies, live births
Khoury 2000	Cross-sectional	Community based, 7200 households	1980	Double first cousins, first cousin 1,2,3 and 4, first cousins once removed, from the family	Number of pregnancies
Luna 1990	Cross-sectional	Community based. 8 villages in an isolated mountain population	NR	Level of CSG NR	Average number of pregnancies, live births
Abdulrazzaq 1997	Cross-sectional	Antenatal, postnatal and immunization centres based interviews and questionnaires	1994-1995	Double first degree, first cousin, first cousin once	Number of abortions and still births

Study	Study design	Data collection	Study period	CSG measure	Fertility Problems outcome measure (duration)
				removed, second cousin, less than second cousin	
Al Husain 1996	Cross-sectional	PHC and antenatal care clinic interviews	1993	Double first cousin, first cousin, second cousin, more distant relative	Abortion, still birth and neonatal death
Asha 1981	Prospective cohort study	NR	NR	Uncle-niece, first cousin, first cousin once removed, second cousin, second cousin once removed, third cousin	Abortion (termination =<28 weeks), still birth (born with no heart beat), neonatal death (within first 28 days of life)
Gharyeb 2014	Cross-sectional	Community based, personally interviewed by structured questionnaires	NR	First degree, second degree, third degree	Abortion (at or before 28 weeks), still births
Islam 2013	Cross-sectional	ONHS data, 2013 household were interviewed	2000	First cousin; father's side, first cousin; mother's side, other; second cousin and beyond	Mean number of pregnancies, live births, number of miscarriage, number of still birth
Saha 1990	Cross-sectional	ANC clinic in the OBGYN department, faculty of Medicine, U of K	NR	First cousins; mother's brother & sister, father's brother & sister, Other type of CSG marriages	Abortion, Still birth, neonatal deaths
Verma 1992	Cross-sectional	Interview in maternity ward in JIPMER hospital	1978	First cousin; MBD or FSD, uncle-niece, other; beyond first cousin	Neonatal death
Yuksel 2009	Cross-sectional	Household interviews, face to face questionnaires	NR	First cousin, others; half first cousin and second degree cousin, distant CSG marriages	Spontaneous abortions, still births

Note. CSG = consanguineous/consanguinity; NR = not reported; PHC = primary health care

Table 3.1.4.

Quality ratings for the 24 included studies on the basis of an adapted Newcastle-Ottawa quality assessment scale

Study	Quality Criterion						Overall rating ^g
	Adequacy of CSG(exposed) measure ^a Max 2 points	Adequacy of control (non-exposed), definition and selection ^b Max 2 points	Comparability of control ^c Max 2 points	Confounders adequately assessed Max 2 points ^d	Adequacy of outcome Fertility Problems measure ^e Max 1 point	None response rate or loss to follow-up ^f Max 1 point	
Edo, 1985	1	2	1	1	1	NR	Average
Hann, 1984	2	2	0	0	0	NA	Average
Tanaka, 1977	2	2	1	0	1	NR	Average
Yamaguchi, 1975	2	2	1	0	1	NR	Average
Bittles, 1993	2	2	1	1	0	NA	Average
Rao, 1979	2	2	1	1	0	NA	Average
Shami, 1990	2	2	0	1	0	NA	Average
Al-Kandari 2007	1	2	1	1	0	NA	Average
Bener 2006	1	2	0	1	0	NA	Low
Blanco 2006	1	2	1	2	1	NA	High
Ciceklioglu 2013	2	2	1	2	1	NA	High
Devi 1981	2	2	0	2	1	NA	High
Fuster 2003	1	2	0	2	1	NA	Average
Khlat 1988	1	2	1	2	0	NA	Average

Study	Quality Criterion						Overall rating ^g
	Adequacy of CSG(exposed) measure ^a Max 2 points	Adequacy of control (non-exposed), definition and selection ^b Max 2 points	Comparability of control ^c Max 2 points	Confounders adequately assessed Max 2 points ^d	Adequacy of outcome Fertility Problems measure ^e Max 1 point	None response rate or loss to follow-up ^f Max 1 point	
Khoury 2000	2	1	1	2	0	NA	Average
Luna 1990	1	1	2	0	0	NA	Low
Abdulrazzaq 1997	1	2	1	2	0	NA	Average
Al Husain 1996	2	2	1	1	0	NA	Average
Asha 1981	2	1	1	2	0	NR	Average
Gharyeb 2014	1	2	1	1	0	NA	Average
Islam 2013	1	2	0	2	0	NA	Average
Saha 1990	1	2	1	2	0	NA	Average
Verma 1992	2	2	1	2	0	NA	High
Yuksel 2009	2	2	1	2	0	NA	High

Note. CSG = consanguineous/consanguinity; NR = not reported; NA = not applicable

^a CSG was adequately assessed when independent validation of the degree of relatedness was assessed or coefficient of CSG(F) calculated, (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as medical/hospital records) and it was representative of the cohort i.e. drawn from the same population (up to 2 points); ^b Controls were adequately assessed when selection was comparable to cases, and CSG was excluded properly in the control population (up to 2 points); ^c Comparability of controls was achieved if exposed/non-exposed were matched or adjustment during analysis conducted. One point for age at marriage and one point for any other confounder (e.g. education) (up to 2 points); ^d Confounders were adequately assessed if they were obtained from records or a blind interview, and one point was given if the same method was used for both groups (up to 2 points); ^e Fertility problems outcome was adequately assessed if independent or blind assessment was stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.) (up to 1 point); ^f Point given if same rate for both groups and <20% loss to follow up reported; ^g The overall quality rating was low (0 to 3 points), average (4 to 6 points), or high (7 to 10 points).

confounders but only one of controlled for confounders. Fertility problems outcome was adequately measured in seven of the included studies, as indicated by blind or independent assessment. Overall the majority (22 of 24, 91.7%) of studies were of high or average quality as per quality assessment in the adapted NOS.

Results reported in Table 3.1.5 indicated that fewer couples in the CSG group had never been pregnant or were childless than in the non-CSG group and the mean number of pregnancies and live births were higher in CSG couples than non-CSG couple. However, CSG couples were more likely to experience miscarriage, stillbirths and neonatal death than the non-CSG couples. Additionally, CSG couples experienced longer time to first birth.

Table 3.1.5.

Proportion of specific outcome in CSG and non-CSG couples in the included studies, (k=24)

Outcome	CSG	Non-CSG
Outcome (number of studies)	Number (%)	Number (%)
Never pregnant (k=3)	92 of 3241 (2.8)	186 of 4120 (4.5)
Childless (K=5)	380 of 6651 (5.7)	717 of 10,240 (7.0)
Miscarriages (k=7)	1069 of 3372 (31.7)	1030 of 3485 (29.6)
Stillbirths (k=7)	243 of 3372 (7.2)	211 of 3485 (6.1)
Neonatal death (k=7)	151 of 2072 (7.3)	144 of 2232 (6.5)
Outcome (number of studies)	Mean (SD), total	Mean (SD), total
Mean time to first birth in years (k=2)	1.8 (24.8), 7011	1.6 (9.4), 2608
Mean number of pregnancies (k=5)	5.0 (3.0), 2735	4.6 (2.9), 4435
Mean number of live births (k=7)	3.9 (2.5), 7433	3.7 (2.3), 10142

Note. CSG = Consanguineous; Non-CSG = none consanguineous

Results of Meta-analyses

Eight meta-analyses were performed and subgroup/sensitivity analysis were conducted where data permitted. Figure 3.1.5 shows the forest plot and meta-analysis result for the two studies investigating mean 'time-to-first-birth' (years). The meta-analysis showed a non-significant overall effect (MD 0.24, 95% CI -0.39 to 0.87) and non-significant heterogeneity ($I^2 = 0\%$. $P = 0.96$). Results indicated that CSG and non-CSG groups were no different in time to first birth (comparable fertility problems).

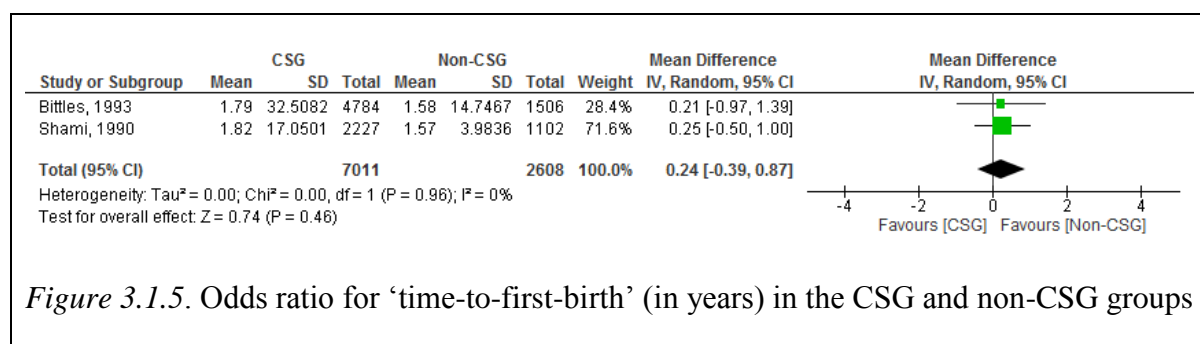
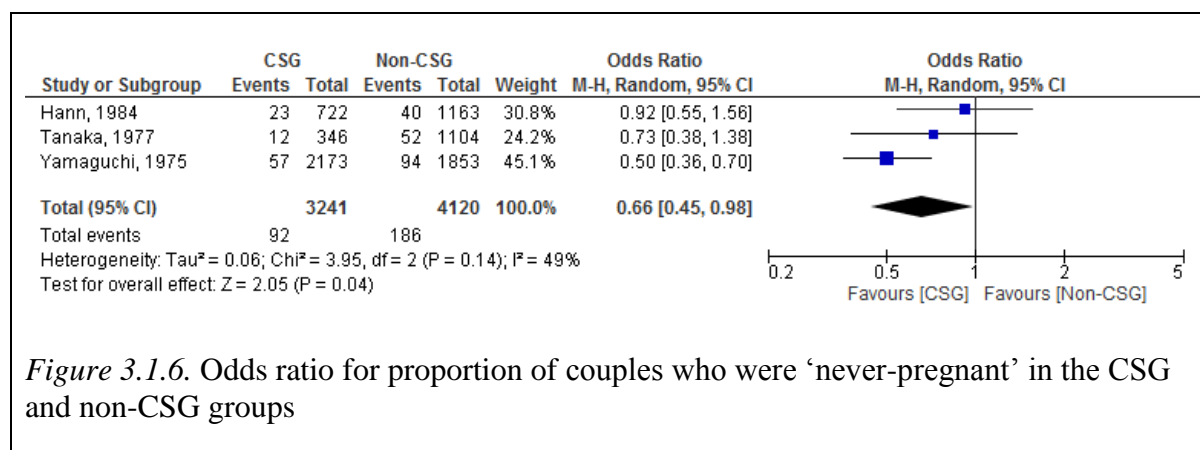


Figure 3.1.6 shows the forest plot and meta-analysis result for the three studies investigating the proportion of couples who were ‘never-pregnant’. The meta-analysis showed a significant overall effect (OR 0.66, 95% CI 0.45 to 0.98), and non-significant heterogeneity (I² = 49%. P = 0.14). Results indicated that the CSG group were less likely to experience never being pregnant than the non-CSG group (less likely to have fertility problems). One study used a duration of 10 years of marriage or lifetime, while the other two used a duration of five years after marriage. A sensitivity analysis excluding the study with longer duration was performed, see Figure 3.1.7. When this study was removed heterogeneity was not significant (I²=0%, P=0.32). However, the overall effect remained significant.



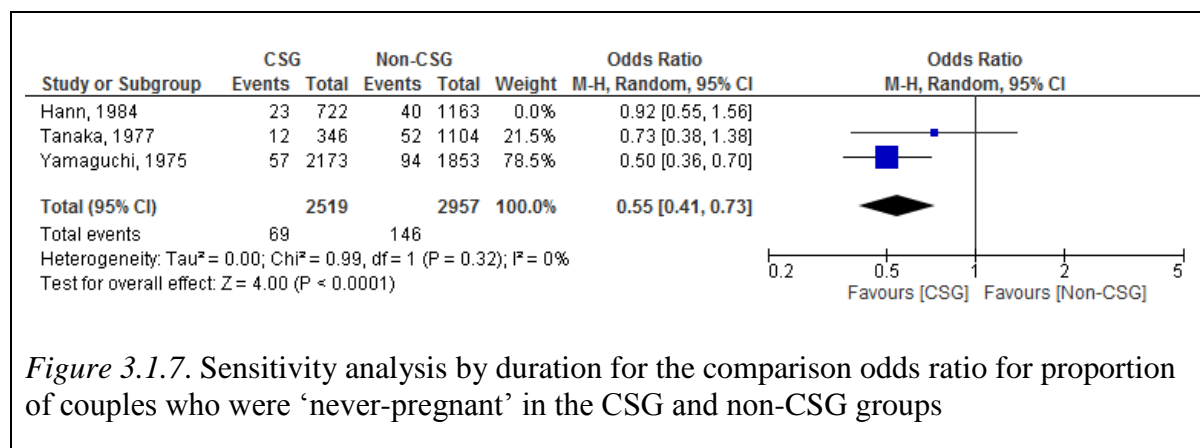


Figure 3.1.7. Sensitivity analysis by duration for the comparison odds ratio for proportion of couples who were 'never-pregnant' in the CSG and non-CSG groups

Figure 3.1.8 shows the forest plot and meta-analysis result for the five studies that investigated the proportion of 'childless' couples. The meta-analysis showed a non-significant overall effect size (OR 0.83, 95% CI 0.74 to 0.95), and significant heterogeneity ($I^2 = 60\%$, $P = 0.04$). Results indicated that the CSG group were equally likely to be 'childless' as the non-CSG group (comparable fertility problems). One study measured childlessness at the end of reproductive life, while the others used five-year durations after marriage (5-9, 10-14, 15-19 and >20). A subgroup analysis separated studies were couples were childless for less than 20 years, from those that were childless for more than 20 years, see Figure 3.1.9.

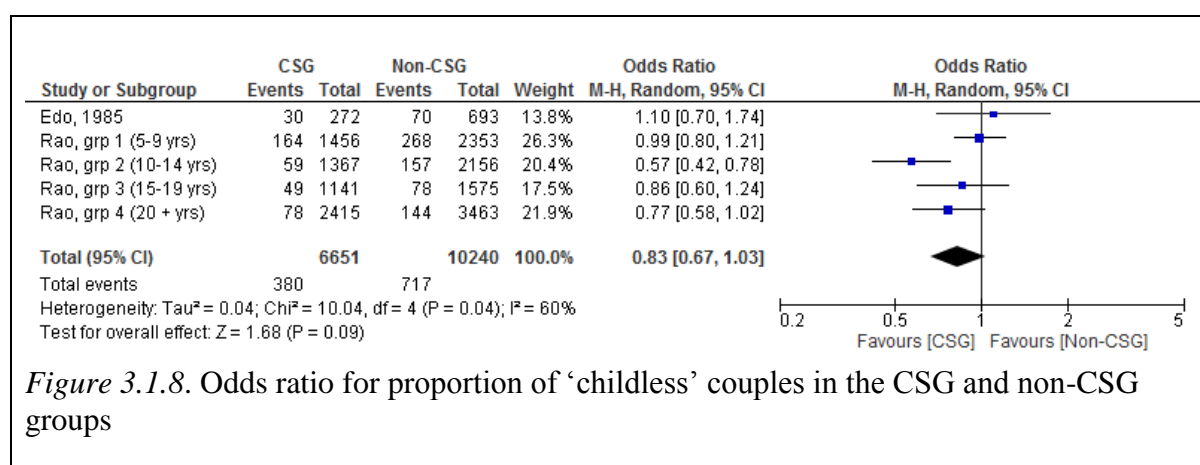
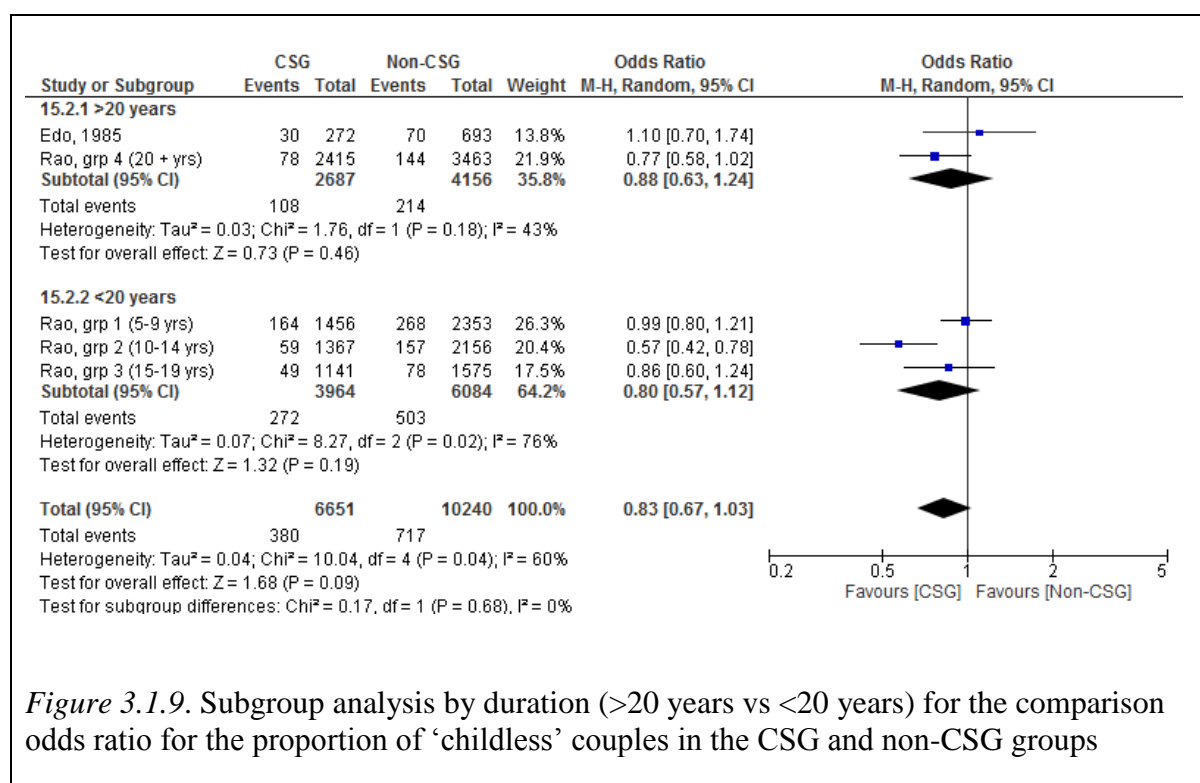


Figure 3.1.8. Odds ratio for proportion of 'childless' couples in the CSG and non-CSG groups

In the subgroup analysis of longer duration (>20 years) heterogeneity was not significant ($I^2=0\%$, $P=0.32$), and the overall effect was not significant (OR 0.88, 95% CI 0.63 to 1.24). The same was true in the subgroup analysis of shorter duration (<20 years), where only the studies with less than 20 years were included (5-9, 10-14 and 15-19 years), heterogeneity remained significant ($I^2 = 76\%$, $P = 0.02$), and the overall effect was not significant (OR 0.86, 95% CI 0.17 to 0.97).

Figure 3.1.10 shows the forest plot and meta-analysis result for the five studies that investigated the mean ‘number of pregnancies’ in the CSG and non-CSG couples. The meta-analysis showed a significant overall effect size (MD 0.40, 95% CI 0.10 to 0.71), and significant heterogeneity ($I^2 = 66\%$. $P = 0.02$). Results indicated that the CSG group were more likely to have pregnancies than the non-CSG group (less likely to have fertility problems).



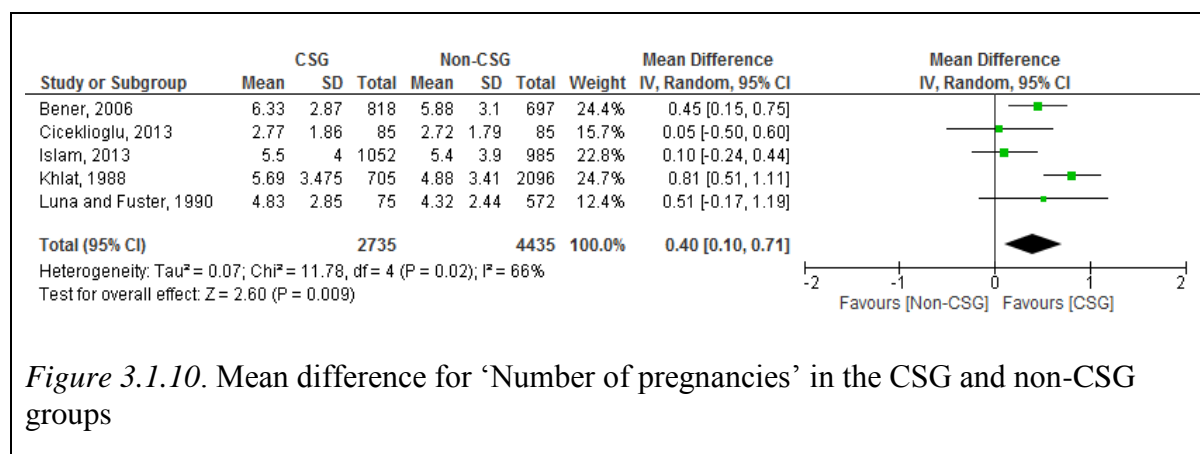
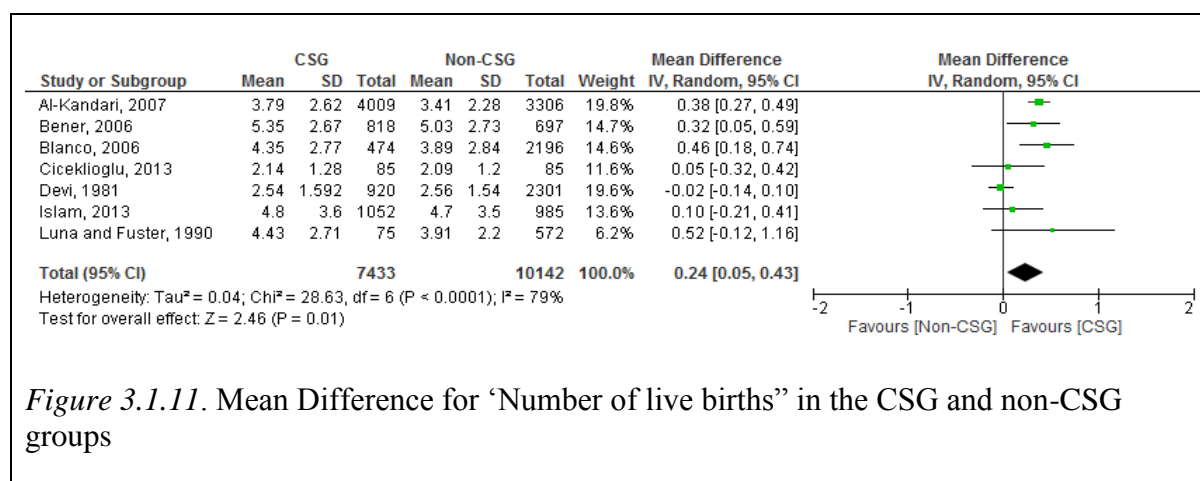


Figure 3.1.11 shows forest plot and meta-analysis result for the seven studies that investigated the mean 'number of live births' in the CSG and non-CSG groups. The meta-analysis showed a significant overall effect size (MD 0.24, 95% CI 0.05 to 0.43), and significant heterogeneity (I²=79%. P < 0.0001). Results indicated that the CSG group were more likely to have live births than the non-CSG group (less likely to have fertility problems). Figure 3.1.12 shows the sensitivity analysis for the mean difference for the 'number of Live births' in the CSG and non-CSG groups. The overall effect size remained significant (MD 0.32, 95% CI 0.21 to 0.44) but heterogeneity was no longer significant (I² = 19%. P = 0.29).



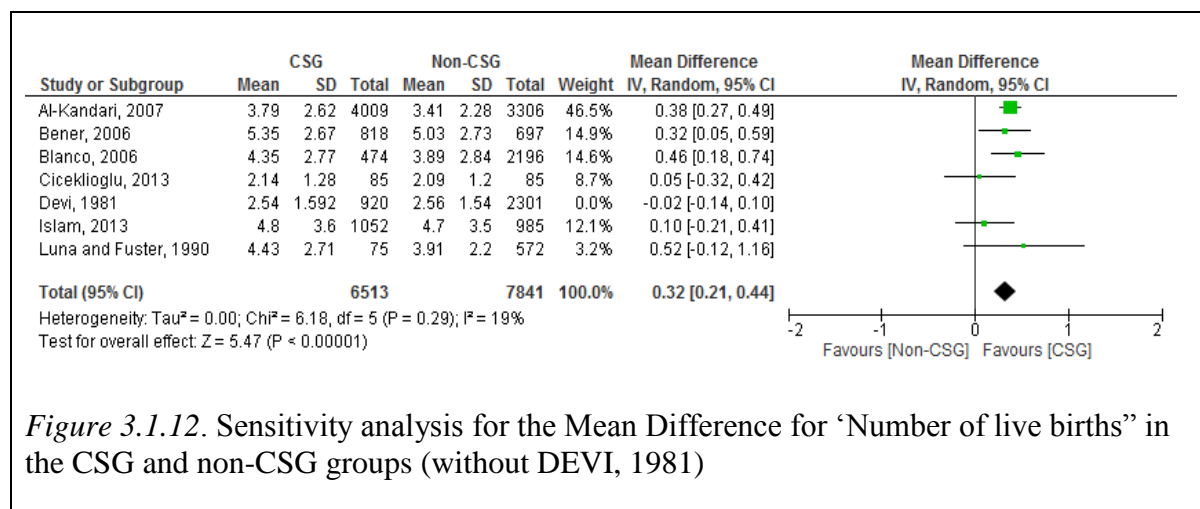


Figure 3.1.12. Sensitivity analysis for the Mean Difference for ‘Number of live births’ in the CSG and non-CSG groups (without DEVI, 1981)

Figure 3.1.13 shows the forest plot and meta-analysis result for the five studies that investigated the proportion of ‘miscarriages’ in CSG and non-CSG groups. The meta-analysis showed a non-significant overall effect size (OR 1.10, 95% CI 0.93 to 1.30), and non-significant heterogeneity ($I^2 = 50\%$, $P = 0.09$). Results indicated that the CSG group were equally likely to have ‘miscarriages’ as the non-CSG group (comparable fertility problems). Figure 3.1.14 shows the forest plot and meta-analysis result for the five studies that investigated the proportion of ‘stillbirths’ in CSG and non-CSG groups. The meta-analysis showed a significant overall effect size (OR 1.28, 95% CI 1.04 to 1.57), and non-significant heterogeneity ($I^2 = 7\%$, $P = 0.36$). Results indicated that the CSG group were more likely to have ‘stillbirths’ than the non-CSG group (more likely to have fertility problems).

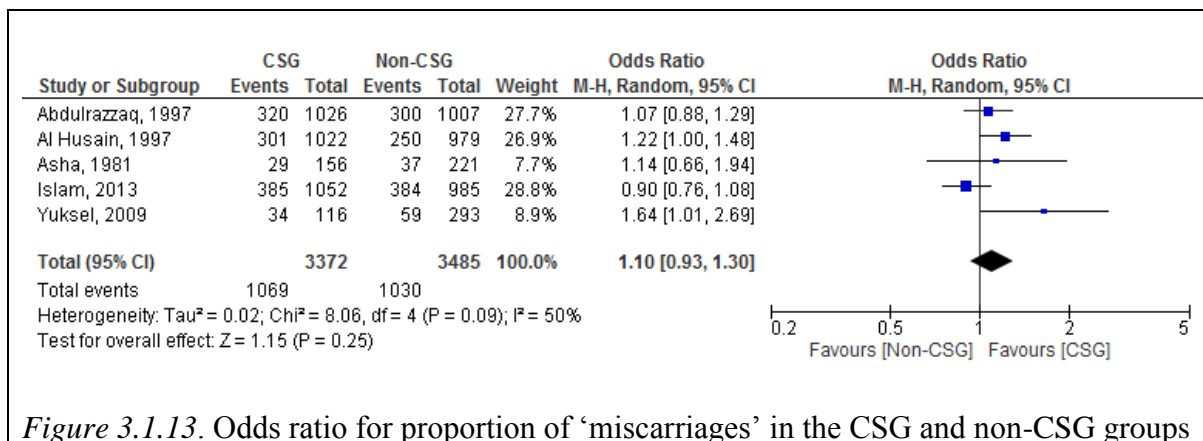


Figure 3.1.13. Odds ratio for proportion of ‘miscarriages’ in the CSG and non-CSG groups

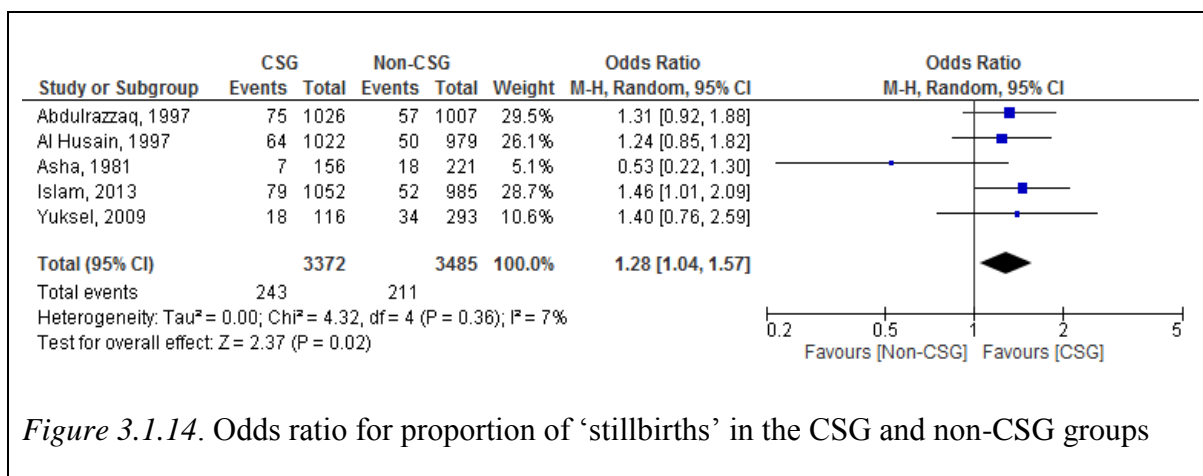
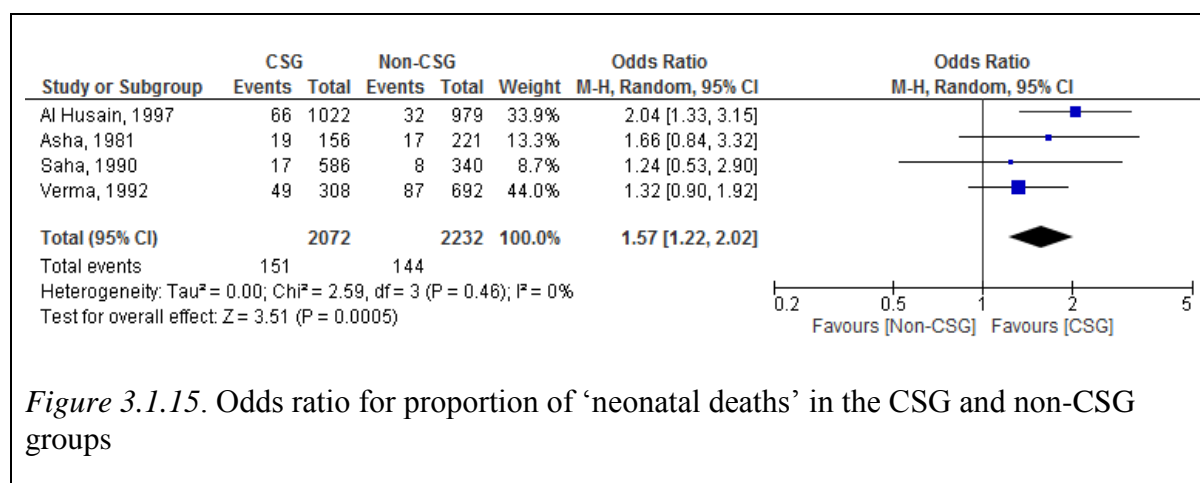


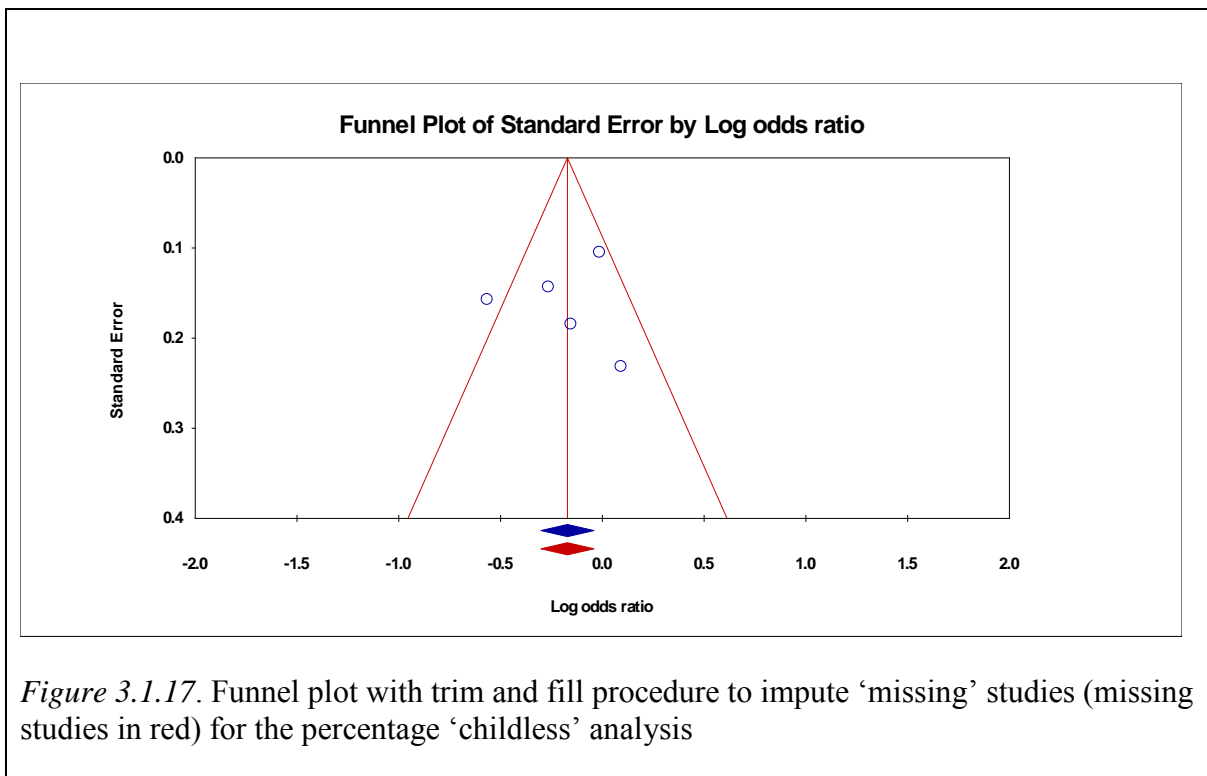
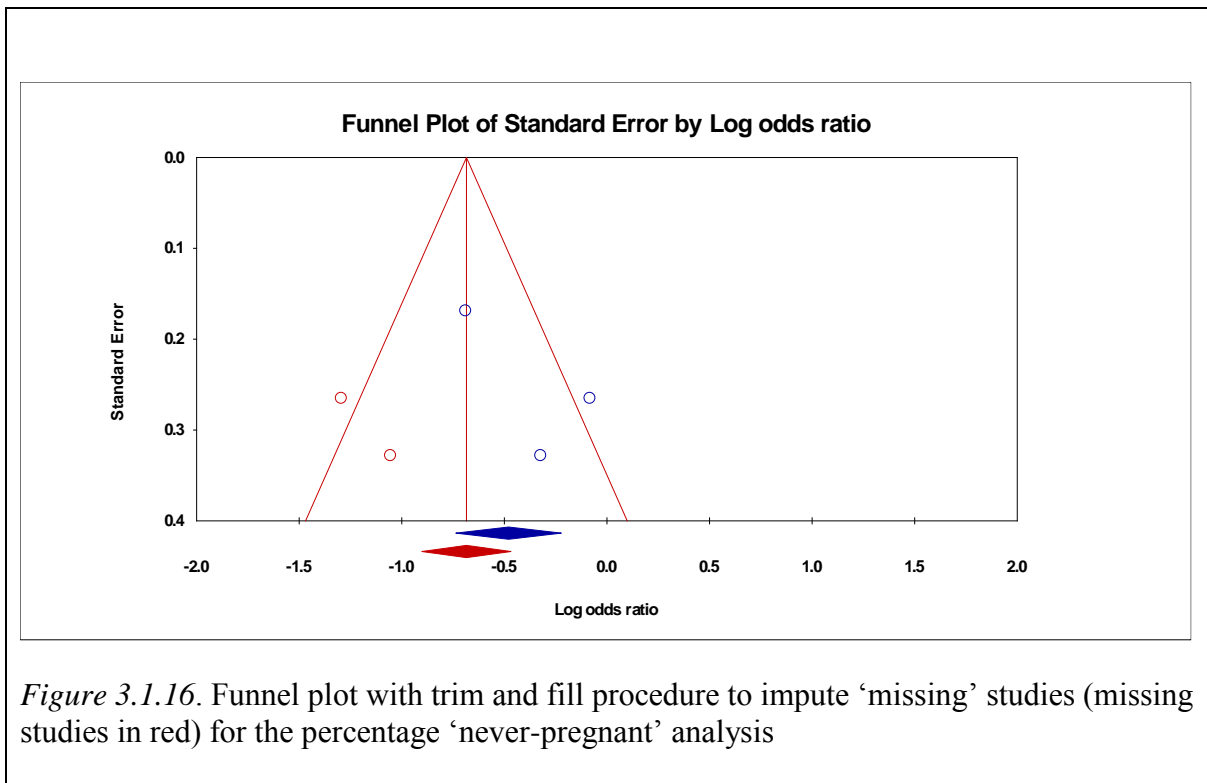
Figure 3.1.14. Odds ratio for proportion of ‘stillbirths’ in the CSG and non-CSG groups

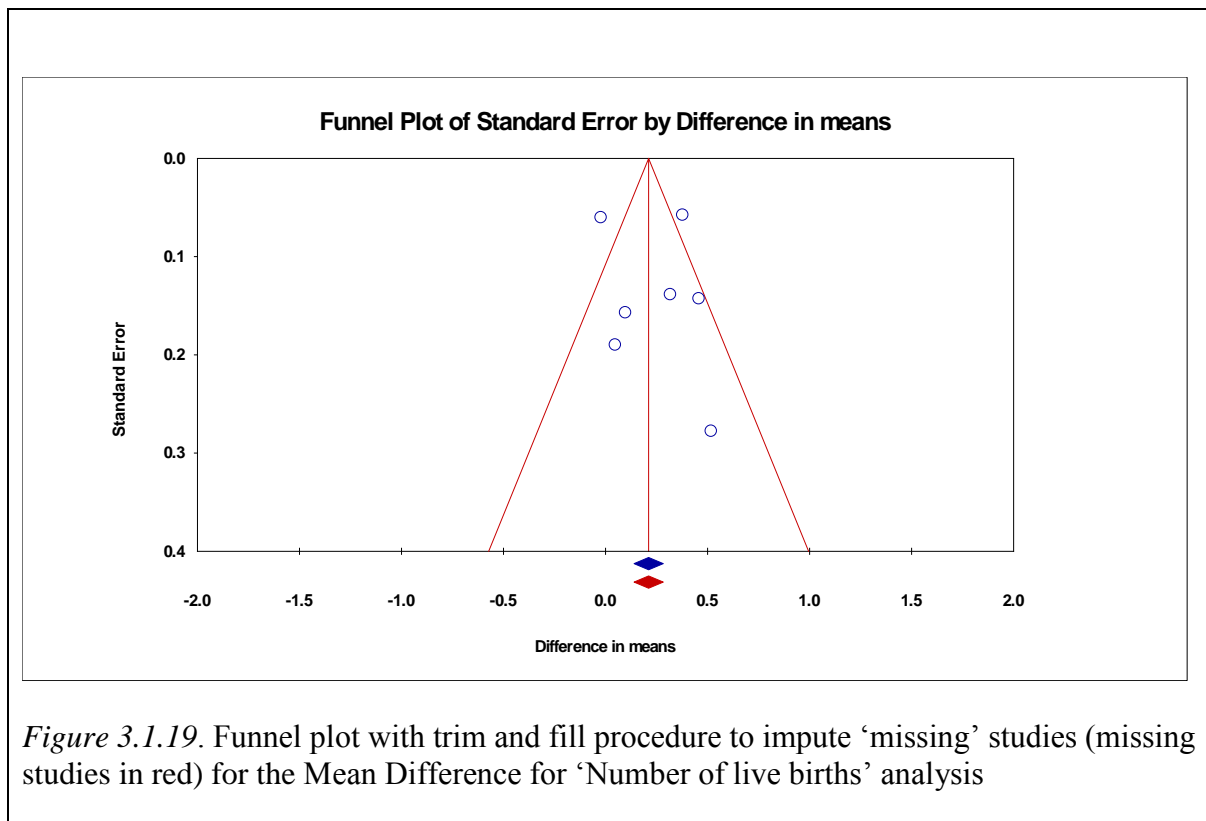
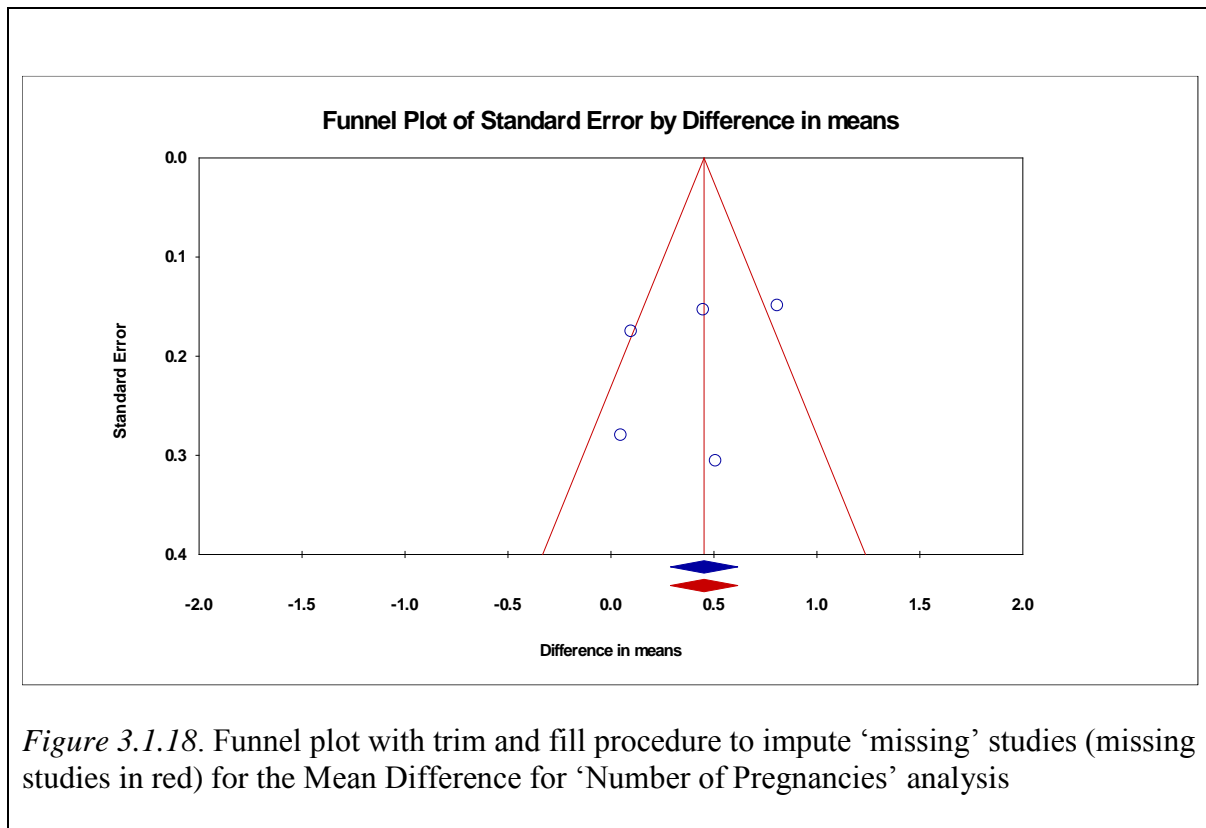
Figure 3.1.15 shows the forest plot and meta-analysis result for the four studies that investigated the proportion of ‘neonatal death’ in CSG and non-CSG groups. The meta-analysis showed a significant overall effect size (OR 1.57, 95% CI 1.22 to 2.02), and non-significant heterogeneity ($I^2 = 0\%$, $P = 0.46$). Results indicated that the CSG group were more likely to have ‘neonatal deaths’ than the non-CSG group (more likely to have fertility problems).



Publication bias assessment.

Publication bias was assessed using funnel plots, Eggers test and trim and fill procedures for seven of the eight analyses, but this was not possible for the ‘time-to-first-birth’ analysis because it comprised only two studies and the software was unable to compute any publication bias analysis. Publication bias was not assessed by visual assessment of funnel plot asymmetry exclusively because there were less than 10 studies (Higgins & Green, 2011, Chapter 10). Egger’s tests performed for the seven meta-analyses were all not significant at $P < 0.05$, indicating the lack of publication bias. Trim and fill was used to estimate the number of ‘missing’ studies and if there were any changes to the magnitude of the pooled effect size if ‘missing’ studies were included. The procedure revealed two missing studies in the analysis ‘never-pregnant’ (Figure 3.1.16) and addition of the ‘missing’ studies reduced the pooled effect size from (0.62 95% CI 0.48 to 0.80) to (0.50 95% CI 0.41 to 0.63), indicating that had the ‘missing’ studies been included the direction of the effect would not change i.e. CSG are less likely to be infertile than the non-CSG group, see Figure 3.1.16. The procedure revealed no ‘missing’ studies in the ‘childless’ analysis (Figure 3.1.17), ‘number of pregnancies’ analysis (Figure 3.1.18) and ‘number of live births’ analysis (Figure 3.1.19).





The procedure revealed two ‘missing’ studies in the ‘miscarriage’ analysis (Figure 3.1.20), and addition of the ‘missing’ studies reduced the pooled effect size from (01.10 95% CI 0.93 to 1.30) to (0.99 95% CI 0.83 to 1.19), indicating that had the ‘missing’ studies been included the direction of the effect would not change i.e. CSG are less likely to be infertile than the non-CSG group. The procedure revealed no ‘missing’ studies in the ‘stillbirth’ analysis (Figure 3.1.21) and ‘neonatal’ analysis (Figure 3.1.22).

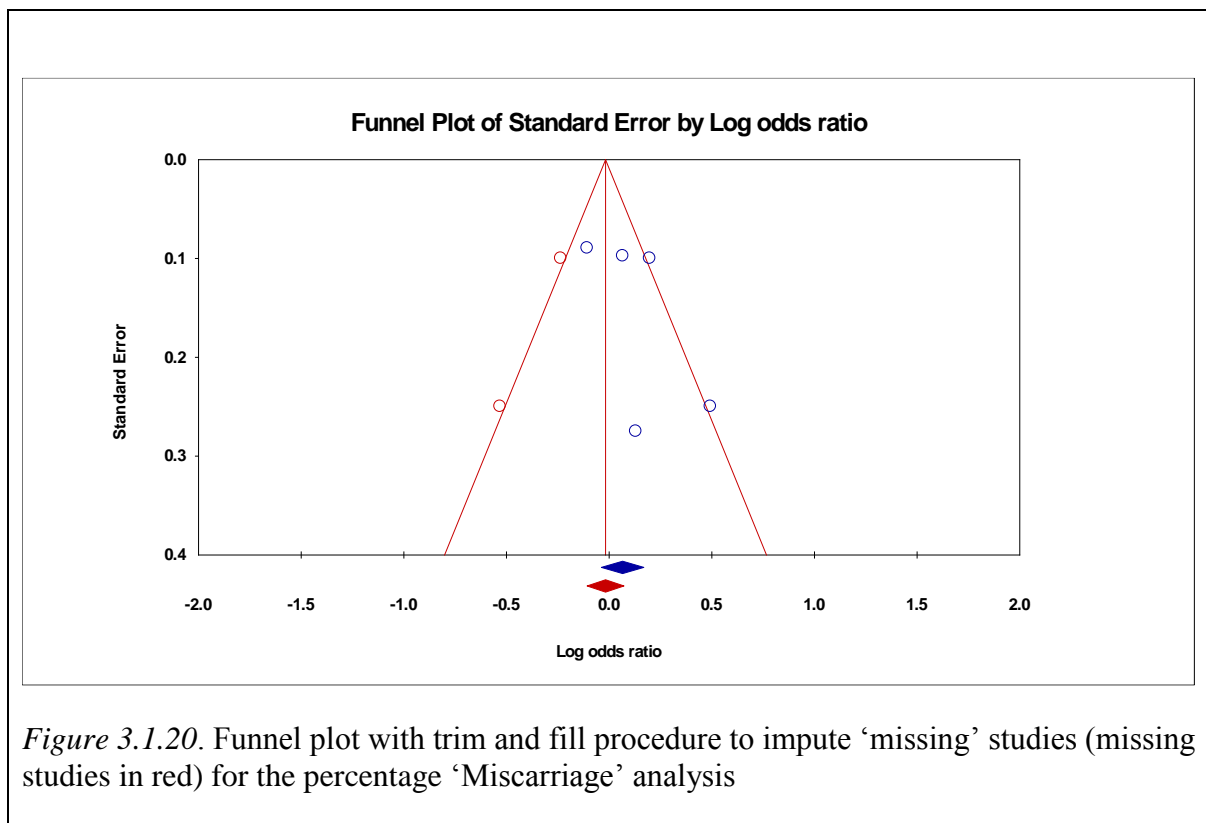
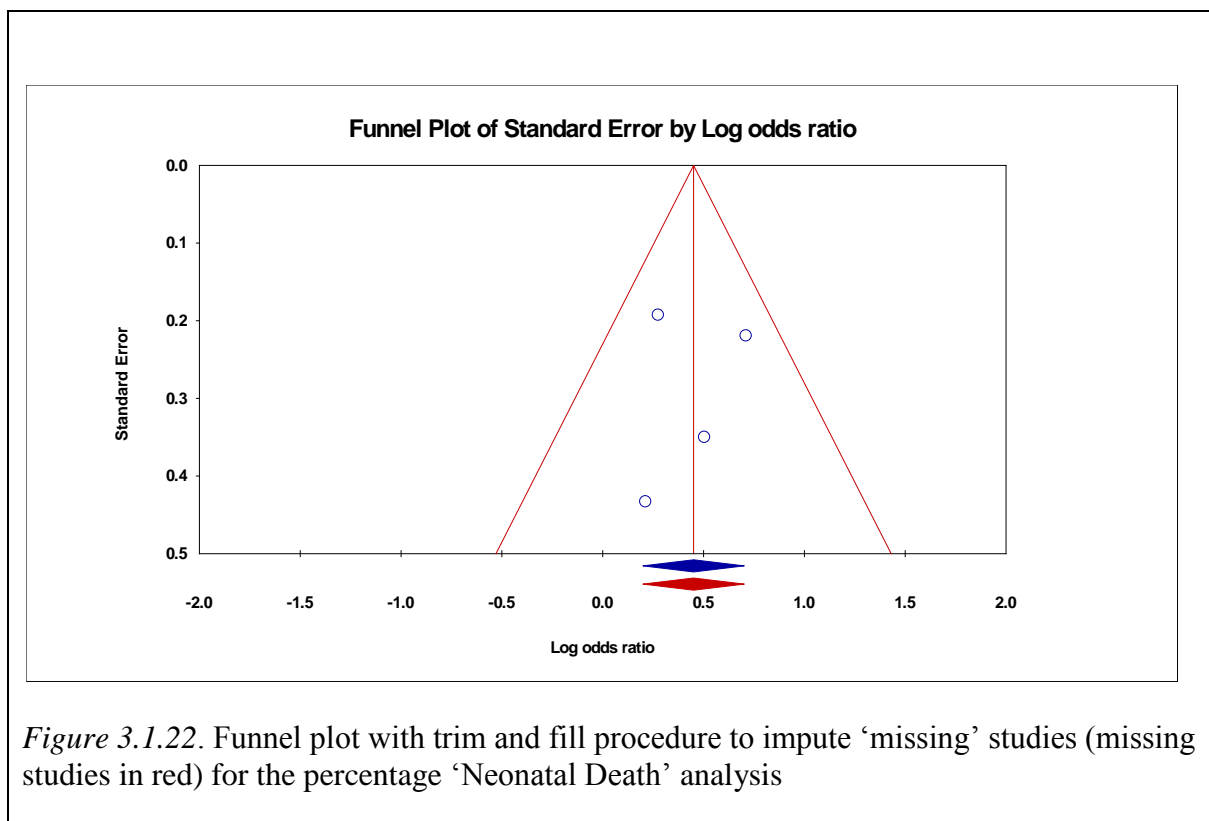
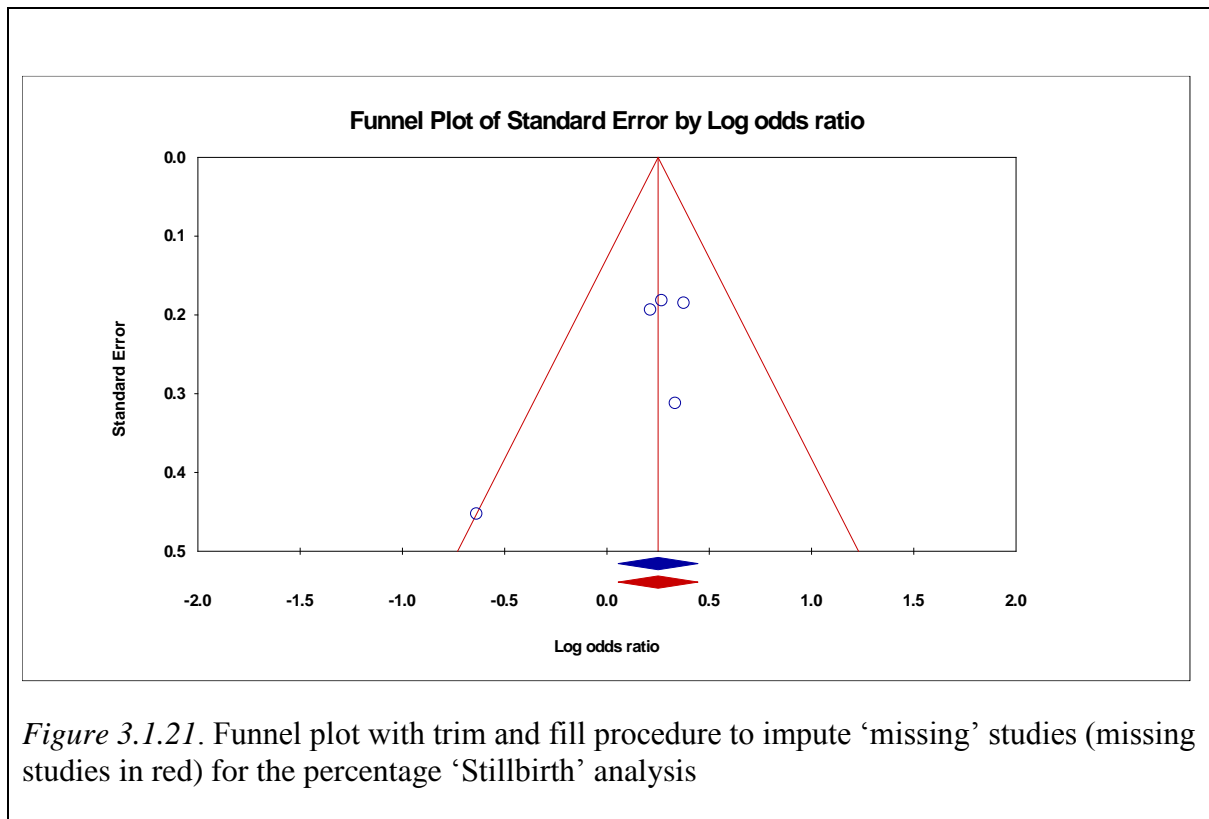


Figure 3.1.20. Funnel plot with trim and fill procedure to impute ‘missing’ studies (missing studies in red) for the percentage ‘Miscarriage’ analysis



Discussion

Principal Findings

The result of the present study suggest that while CSG couples were more likely to achieve pregnancy and live birth, they were equally as likely to be childless and to have miscarriages. On the other hand, they were more likely to have adverse effects such as stillbirths and neonatal deaths. Additionally, the CSG group did not take longer to have live birth than the non-CSG group, indicating that in the short-term CSG did not exert an impact on ability to have a live birth. It can be inferred from these results aggregated together that CSG may facilitate pregnancy but hinder fertility through perinatal losses. The results of the review are important because they imply that women in CSG partnerships will not experience problems achieving pregnancy but ultimately have similar numbers of children due to more distressing reproductive events like stillbirths and neonatal deaths than women in non-CSG partnerships. Future research should include longitudinal cohort studies that follow CSG couples over time to fully capture the effects of consanguinity.

A possible explanation for the increased ability to become pregnant and have a live birth in the CSG group is through the increased compatibility of gametes produced by CSG as proposed in the literature (Shami et al., 1990; Hann, 1984; Bittles, 1991), pathway 1, Figure 3.1.3. A second explanation for the enhanced ability to get pregnant could be due to the mechanism of factors like age and age at marriage, since CSG couples tend to be younger and married at a younger age in the samples as shown in the characteristics of the primary studies reviewed (where available), pathway 2, Figure 3.1.3. The younger age at marriage could be relevant for two reasons: (a) fertility is higher at younger ages, and peaks in the early 20s [19-26 years] (Dunson, Colombo & Baird, 2001), (b) younger age leads to a longer reproductive span during which the couple can eventually achieve pregnancy. A third explanation for the greater number of pregnancies could be due to reproductive compensation during which CSG couples compensate for post-natal death caused by CSG (Bittles et al.,

2002), pathway 3, Figure 3.1.3. Current meta-analytic results showing more pregnancies and live births in CSG couples indicated that one or many of these pathways are in effect, which pathway, however could not be determined due to lack of primary studies. Current meta-analytic evidence also supports reports of post-natal outcomes like stillbirths and neonatal deaths, pathways 4, b and c, Figure 3.1.3. However, current meta-analysis differed from literature (Shami, Schmitt, & Bittles, 1990; Hann, 1984; Bittles, Mason, Grenne & Rao, 1991) indicating more negative gestational outcomes like miscarriage, pathway 4 a, Figure 3.1.3. Pathway 4 d (death of offspring) was not assessed due to lack of such studies in the current search. Therefore, the current results support enhanced ability to achieve pregnancy through pathways 1, 2 and/or 3, confirm pathways 4 b (stillbirths) and c (neonatal deaths) as pathways that lead to more fertility problems. The results indicating similar number of miscarriages but increased likelihood of stillbirths and neonatal deaths indicates that the congenital effects exert more impact after gestation. However, this should be interpreted with caution because very early miscarriages may be more difficult to determine than stillbirths and neonatal deaths. The results aggregated together suggested that what advantage CSG offers of younger age at marriage, reproductive compensation and gamete compatibility must level off as indicated by the comparable childlessness as suggested in the literature (Shami, Schmitt, & Bittles, 1990; Hann, 1984; Bittles, Mason, Grenne & Rao, 1991). This levelling off is likely because of counter effects of the increased risk of stillbirth and neonatal deaths due to congenital abnormalities that occur more in CSG couples as a results of the cumulative effect of recessive genes pooling over time (Bittles & Black, 2010; Bhasin & Shampa, 2012; Hamamy, 2012).

In the present study the effect of CSG on fertility was examined in a set of meta-analyses of observational studies. This systematic approach demonstrated that CSG was associated with increased likelihood of stillbirth and neonatal deaths but less likelihood of

never achieving pregnancy. However, a causal relationship could not be confirmed, nor could a specific mechanism of action be specified. Therefore, if we apply the ‘Bradford Hill criteria’ noted in the General Methods (pp. 55), we can see that three of the nine apply to the current review and enhance confidence in the causal relationship between CSG and fertility problems. The criterion of ‘Biological gradient’ was met because reports in the literature show that the closer the relationship (especially first degree cousins) the more likely the impact on fertility (Bittles et al., 2002; Bittles & Black, 2010; Hussain & Bittles, 2004), however it was not possible to support this in the current meta-analyses due to lack of data. The criterion of ‘temporality’ was met since CSG occurs before sexual activity in the societies where it is practiced and consequently all reproductive output is considered after marriage. Finally, the criterion of ‘plausibility’ was met because the model set forth in the literature regarding pooling of recessive genes leads to increase likelihood of morbidity and mortality in offspring (Bittles & Black, 2010; Hamamy, 2012) as well as the gamete compatibility leading to increased likelihood of pregnancy (Hussain & Bittles, 2004; Bittles et al., 2002) are biologically sound and supported by the current meta-analyses.

Justification for not including CSG in the original FertiSTAT.

Results demonstrated that CSG provided an advantage at the time of pregnancy, as suggested in the literature (Hussain, 2004; Bittles, 2002). Since FertiSTAT is used to inform women about risk factors associated with a reduced ability to become pregnant, the results of the current meta-analyses indicated that inclusion of CSG in FertiSTAT as a new risk factor would not increase predictive ability of the tool in developing countries.

Implications of Findings

Although results indicated that CSG would not improve prediction of impaired ability to achieve pregnancy, awareness of the risks associated with it should nevertheless be

communicated to couples due to the corroboration of the reported increased likelihood of postnatal mortality (stillbirths and neonatal deaths) among women in CSG partnerships. Therefore, if the adapted FertiSTAT is to be used to inform women of factors that could potentially hinder their ability to have a live birth, then CSG should be included in the adapted version because it was found to be associated with increased likelihood of stillbirth and neonatal deaths.

The implication of the present review is that couples should be counselled before marriage and/or becoming pregnant about the potential effects of CSG on the likelihood of pregnancy and postnatal outcomes. Couples should be informed that although CSG may be associated with an enhanced ability to achieve pregnancy, it will not ultimately increase the number of children they will have (Hussain & Bittles, 2004 and Bittles et al., 2002), and that they are more likely to experience adverse outcomes such as stillbirth and neonatal death due to genetic abnormalities in the offspring (Bittles & Black, 2010; Bhasin & Shampa, 2012; Hamamy, 2012). Couples need to be informed that the closer the biological relationship between father and mother the more likely their progeny will inherit recessive genes that may be harmful (Bittles et al. 1991; Bittles & Black 2010; Hamamy et al. 2011; Hamamy, 2012). These issues are best communicated via a comprehensive pre-pregnancy care package. Pre-pregnancy care covers the delivery of medical, behavioural and social interventions to women and couples prior to pregnancy, with the aim of improving health and reducing risk factors (behavioural and environmental) that impact on maternal and child health (Preconception care: maximizing the gains for maternal and child health, WHO, 2013).

Strength and Limitations in Included Studies

The heterogeneity in study methodology, outcome measures and sample size in included studies could affect the comparability of these studies and the generalizability of the results of this review.

Heterogeneity in CSG measure (e.g. varying degrees of relatedness), fertility problems outcome (e.g. different duration of childlessness, time to first birth, inability to become pregnant), study design (e.g. cohort and cross-sectional) and data collection methods (e.g. records and interviews) can affect the practical applicability of the results. However, issues of heterogeneity were dealt with both in comparing different outcomes separately and through subgroup analysis. The quality of each study independently did not appear to affect the overall results of the review since the majority of studies were of sound quality.

Bias relating to the primary studies included selection bias, information bias and recall bias. It can be assumed that since the selection of participants was from the same sample and information was gathered using the same method for both the exposed and non-exposed groups in all the studies, that selection and information bias may not affect results significantly. Recall bias can affect the internal validity of results where data was collected in interviews that require recall of old events, but this is more substantial for recall of details (Hassan, 2005). Thus, recall bias might not have been considerable because the interviews did not require-- recall of details e.g. period of childlessness or degree of relatedness with spouse. Bias due to confounder is a major limitation of the studies included, because matching the groups for confounders or including confounders in the analysis was not reported in any of the included studies. The most important confounder 'age at marriage' which increases the reproductive span was only recorded in three studies. There could have been an unequal distribution of other confounders in the exposed and non-exposed groups but this was not reported in the studies. The effect of confounders like age, age at marriage, and duration of marriage might have influenced the relationship between CSG and fertility problems reported in these studies.

Another limitation relating to the primary studies was the use of observational studies. In the case of CSG, randomization would not have been possible or ethical, therefore the

most rigorous design would be cohort studies, followed by case-control and cross-sectional (Mann, 2003). Cohort studies are thought to be superior to cross-sectional designs in establishing cause and effect relationships because they measure events in chronological order (Mann, 2003). Cross-sectional studies can be a good starting point to identify associations that can then be followed by more rigorous studies (Mann, 2003). Four of the seven studies were cohort studies and the other 20 were cross-sectional, therefore, the results of meta-analysis can only be used to infer association. However, due to the adequate quality, the large sample sizes and the diverse samples of the studies included at least the nature and direction of the effect of CSG on fertility problems can be accepted. Additionally, the low cost of cross-sectional studies might make them the most feasible choice in resource constrained settings, thus research from developing countries may be confined to this design. Ideally the research that could help shed light on the nature of the impact of CSG on different aspects of the reproductive process is a longitudinal cohort study that follows couples in CGS and non-CGS (of varying degree of consanguinity) partnerships over time to determine the number of pregnancies, pregnancy losses, stillbirths and health outcomes for the progeny of these unions. Such a study should incorporate genetic testing for the couple as well as all offspring. Additionally, it should include controls that are matched for confounders such as age, age at marriage, education, socioeconomic status and other factors that may moderate or mediate the effect of CSG on reproduction. If matching is not possible these confounders should be included in multivariate analysis.

Future Research

To fully capture the effects of CSG future research needs to consider its effect on ability to become pregnant separately from ability to carry to term and deliver a live baby. Studies that use live birth as the outcome do not permit inferences to be made as to whether

the effect is on ability to become pregnant, carry to term or delivery.

Future research to unravel the effect of CSG on fertility problems requires longitudinal cohort studies to examine the CSG couple's reproductive process to examine outcomes like duration to first pregnancy, early miscarriage, gestational problems and birth outcomes as well as genetic problems in offspring. Future research that includes genetic testing of parents and offspring should consider at a molecular level an understanding of the reasons for the higher pregnancy rate. Such research can investigate the hypothesis of compatible uniting gametes, as well as factors affecting overall fertility such as pooling of recessive genes, reproductive span and reproductive compensation. Studies could match groups for or include in analysis confounders like age at marriage to investigate reproductive span and compensation.

Conclusion

There have been many theories to explain the paradox between the higher rate of morbidity and mortality in the offspring of CSG couples and the overall equivalent if not higher rates of fertility (number of live births). Our results helped shed light on this issue by separating the ability to become pregnant from being childless and by examining postnatal outcomes. It can be concluded from the results that factors such as gamete compatibility combined with longer reproductive span and reproductive compensation can increase the likelihood of pregnancy but the pooling of recessive genes balances out this advantage through increased stillbirths and neonatal deaths, so that the risk of childlessness is similar in both CSG and non-CSG couples. In light of the results, inclusion of CSG as a new risk factor for fertility problems in the adapted FertiSTAT cannot be justified since it is not associated with reduced ability to achieve pregnancy.

Study 3.2: Systematic Review and Meta-analysis of Observational Studies Examining the Association of FGM/C and Fertility Problems

Introduction

Female genital mutilation/cutting (FGM/C) was one of the risk factors identified through the process of adapting the FertiSTAT and was endorsed by the experts in Study 2.1 (Chapter 2, pp. 25). The validity of this risk factor as a predictor of fertility problems was examined in the current systematic review using the operational definitions of fertility problems and risk factor applied in the original development of FertiSTAT (Bunting & Boivin, 2010).

Description of FGM/C

FGM/C also known as female circumcision or cutting is a cultural practice in over 25 African countries and some Asian regions (Toubia & Sharief 2003). The World Health Organization (WHO) defines FGM/C as “all procedures that involve partial or total removal of the external female genitalia or other injury to the female genital organs for non-medical reasons” (WHO, 2014, FGM/C Fact sheet No241). Table 3.2.1 and Figure 3.2.1 show the WHO classification of the FGM/C procedure into four categories. Type I and II are milder forms of the practice, while Type III, also known as infibulation is more severe, involves suturing and is mostly practised in north-eastern Africa, predominantly in Djibouti, Eritrea, Ethiopia, Somalia and Sudan (Yoder & Khan, 2008). Type IV is any other alteration to the female genitalia that is not classified as I, II or III. It is important to note that a woman who has undergone infibulation will require defibulation for childbirth (i.e., incision to the vulva to open the vagina) and re-infibulation post birth (i.e., re-suturing of the vulvar opening).

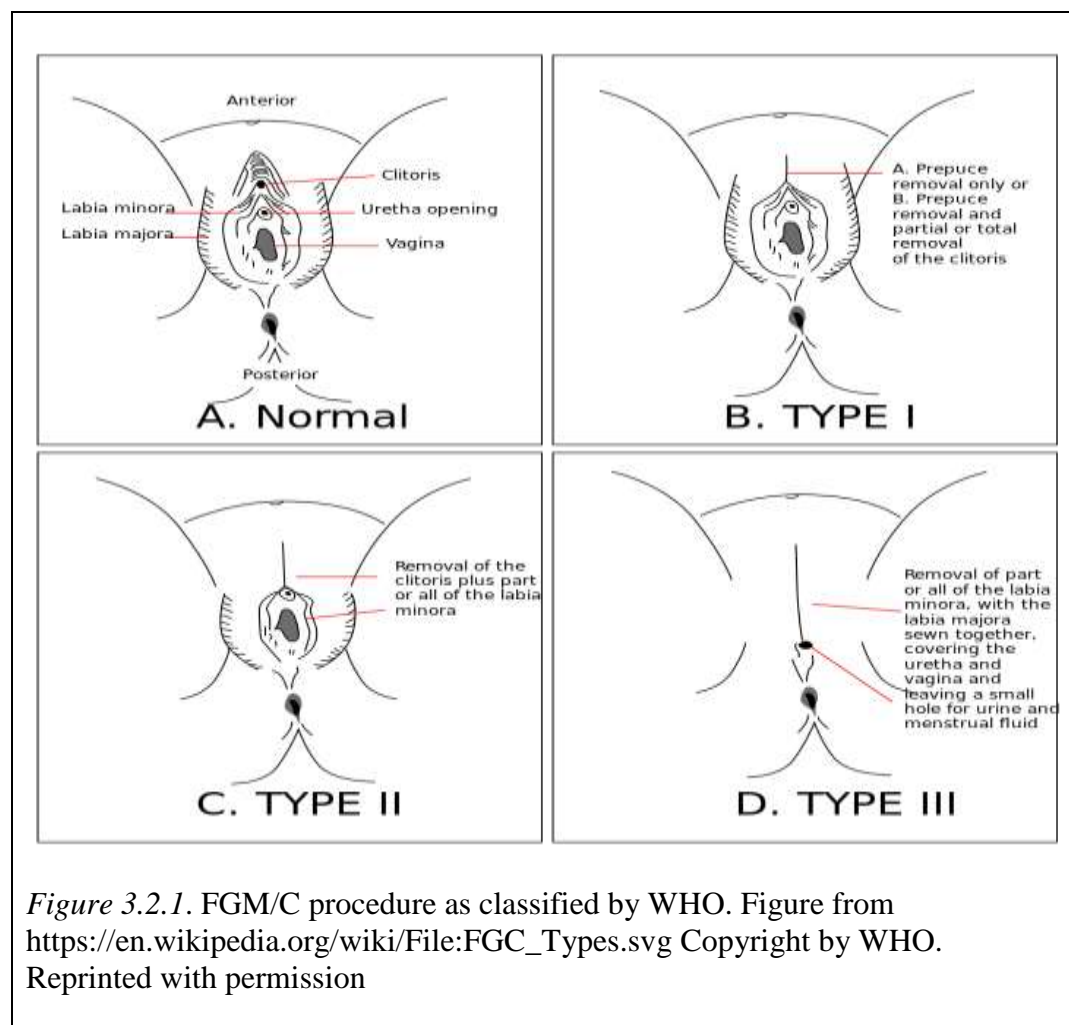
According to the Royal College of Obstetricians and Gynaecologists' (RCOG) guidelines on FGM/C, the procedure is usually performed between infancy and 15 years, and it is usually performed by traditional practitioners with little or no medical training. The procedure is usually performed using crude instruments such as knives, scissors or razor blades and without anaesthetics. The term *medicalization* of FGM/C is used to refer to cases where a trained healthcare provider performs the FGM/C procedure or reinfibulation as reported by the United Nations Children's Emergency Fund (UNICEF, 2013). The medicalization of the procedure is becoming more prevalent especially in Egypt, Sudan and Kenya (RCOG, 2015).

Table 3.2.1.

WHO classification of FGM/C

Type	Definition
Type I	Clitoridectomy; partial or total removal of the clitoris (a small sensitive and erectile part of the female genitals) or, in rare cases, only the prepuce (the fold of skin surrounding the clitoris)
Type II	Excision; partial or total removal of the clitoris and labia minora with or without removal of the labia majora (the labia are “the lips” that surround the vagina)
Type III	Infibulation; narrowing of the vaginal opening through the creation of a covering seal. The seal is formed by cutting and repositioning the labia minora or majora with or without removal of the clitoris
Type IV	Other; all other harmful procedures to the genital for non-medical reasons e.g. pricking, piercing, incision, scraping and cauterising the genital area

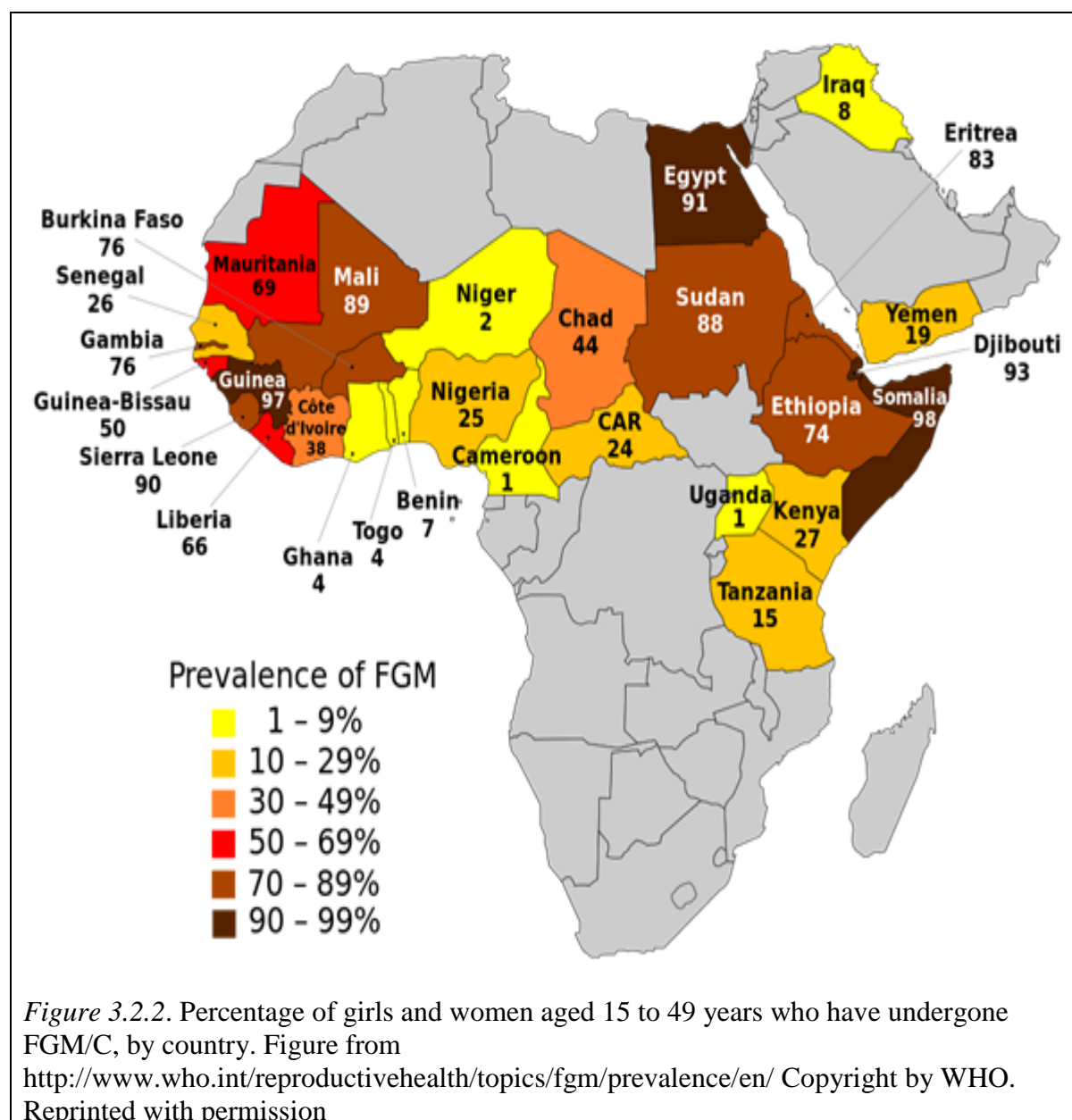
Note. WHO = World Health Organization; FGM/C = Female Genital Mutilation/Cutting



Although awareness about FGM/C and its impact on female health has increased over the past 20 years this has yet to translate into measurable changes in prevalence (Toubia & Sharief 2003). The practice of FGM/C may have stemmed from a patriarchal structure of social control of sexuality and fertility and women are the primary social group to suffer from it, but it also appears that women are also the perpetrators of the practice (Toubia & Sharief 2003). The prevalence of female circumcision in Africa differs from population to population as reported by the joint program of the United Nations Population Fund and UNICEF (UNFPA-UNICEF, 2014). Prevalence is highest in North East Africa, with the highest reported rate in Somalia (98%), followed by Egypt (91%) and Sudan (88%), see Figure 3.2.2. The prevalence is also very high in Northern West African countries like Guinea (97%) and

Mali (89%), while it is much lower in countries like Nigeria (25%) and almost non-existent in southern Africa (USAID, 2008; UNFPA-UNICEF, 2014).

Information sheets that summarize evidence on the different types of violence against women published by the WHO's Department of Reproductive Health Research (RHR) and the Pan American Health Organization (PAHO) in 2012 include data on FGM/C. This material includes information on cultural, religious and social factors that predispose girls to FGM/C i.e. factors that influence their families to subject them to the procedure (WHO, RHR & PAHO, No. 12.41, 2012). Factors include social pressure from extended family/society, rural living, being uneducated, being Muslim, having undergone FGM/C themselves and having no exposure to mass media. Attitudes that perpetuate the practice include the idea that FGM/C preserves purity and cleanliness and the belief among some women that it improves sexual pleasure for their husbands. It is also noted that the education of the mother has a protective effect for her daughters, which is similar to that seen in other cases of violence against women. However, this positive impact of education is not always evident. In some locations the effect was reversed with the more educated mothers more likely to subject their daughters to FGM/C (WHO, RHR & PAHO, No. 12.41, 2012). These mixed results are also reported in a study in Sudan that shows that even within the same country education of the family/mother could have a different impact depending on region (Mazharul Islam & Uddin, 2001). The authors interviewed women from different regions within Sudan on attitudes and included factors such as education and socio-economic status (SES) of the family and whether the mother was cut. Results indicated that in the rural area sampled education had a protective effect while in the urban (low income) suburb of the capital more education was linked to more FGM/C (Mazharul Islam & Uddin, 2001). These mixed results signify the importance of considering the effect of education and SES in any analysis of the effects of FGM/C to help understand if such factors have a mediating and/or protective effect.



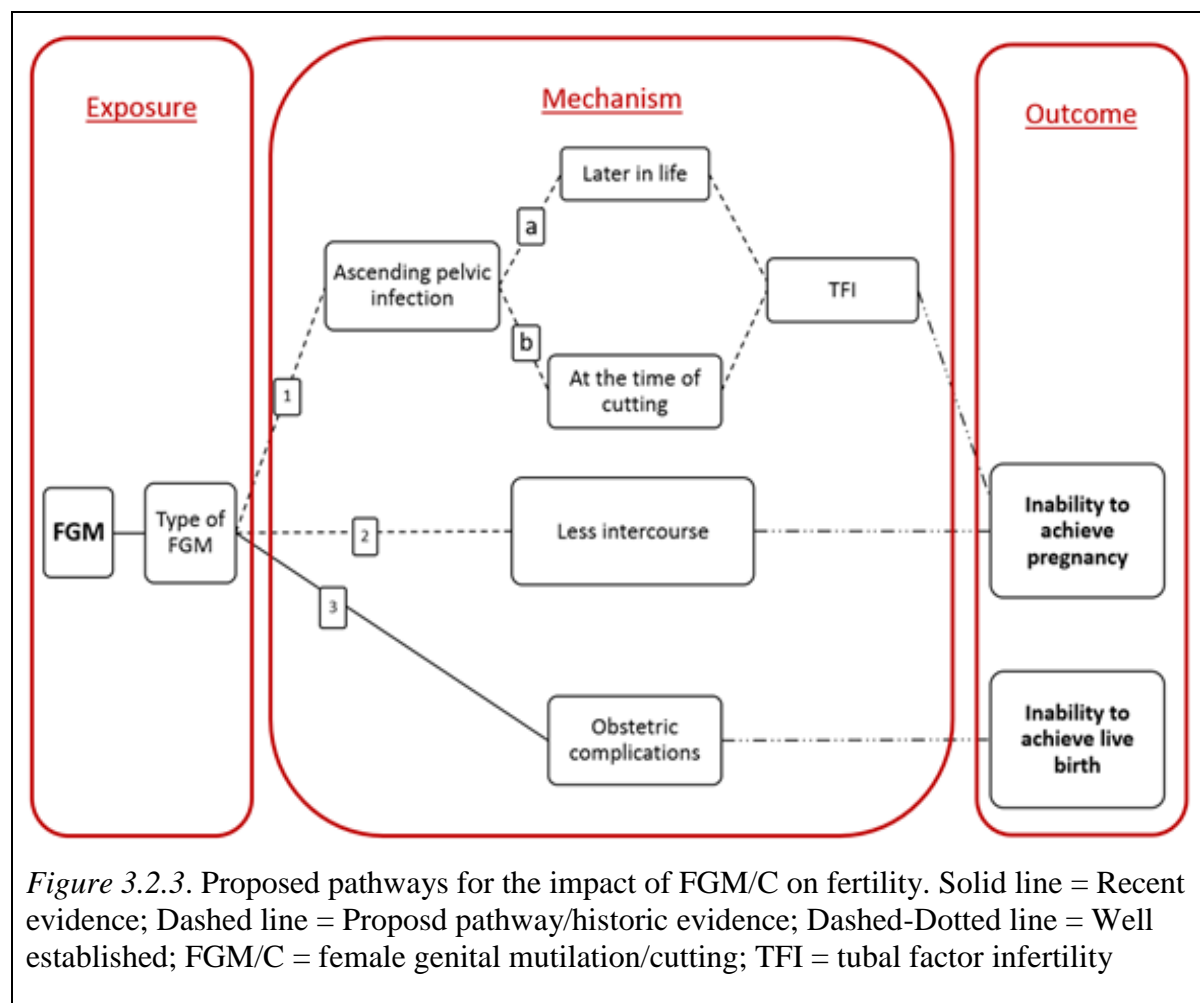
Plausible Mechanisms to Explain why FGM/C Could be Associated with Fertility Problems

Fertility problems have been reported as long-term health consequences of FGM/C in numerous publications including guidelines such as the RCOG, the Canadian Clinical Practice Guidelines, and the WHO (RCOG, 2015; Perron, Senikas, Burnett, & Davis, 2013; A Systematic Review of the Health Complications of Female Genital Mutilation, WHO, 2000). Injuries or infections to the female reproductive tract have been proposed historically

as possible biological pathway through which FGM/C (any form) may lead to difficulty becoming pregnant or carrying a pregnancy to term since the late 1960s (Shandall 1967; Lenzi 1970; Belsey 1979).

Based on information obtained from the literature it was clear that the impact of FGM/C on fertility was likely to be through an indirect effect. Several plausible mechanisms have been suggested in the literature: (1) ascending pelvic infection, at the time of the FGM/C procedure or later in life (not at the time of the procedure) that causes tubal damage, (2) lack of intercourse due to difficult or painful penetration, and (3) obstetric complications e.g. prolonged labour (Obermeyer, 2005; RCOG, 2015; Reisel & Creighton, 2015; WHO study group on female genital mutilation and obstetric outcome, 2006). These mechanisms were used to conduct a potential pathways model depicted in Figure 3.2.3.

In the first mechanism, infection at the time of the procedure appears to be plausible because the vagina of the prepubescent girl is low in oestrogen and the epithelium is thin, making the girl more susceptible to infection (Farrington, 1997; Mroueh & Muram, 1999). In the absence of this protective hormonal environment the infection can then ascend to the uterus and fallopian tubes and, if left untreated, can lead to pelvic inflammatory disease (PID) and subsequently tubal factor infertility (TFI). PID is an infection of the female reproductive tract and adjacent pelvic structures that is unrelated to previous surgery or pregnancy (McCormack, 1994). If PID is left untreated then the infection can ascend from the uterus to the upper genital tract i.e. the fallopian tubes causing obstruction and consequently TFI (Land & Evers, 2002; Sciarra, 1997). PID has been reported to be primarily caused by STIs e.g. chlamydia and gonorrhoea (Rhoton-Vlasak, 2000).



In addition to infection at the time of the procedure, infection later in life (long-term consequence) seems plausible due to change in anatomy (suturing forms a skin fold that is not accessible for cleaning that may harbour harmful microorganisms) that may render the woman at an increased risk of gynaecological infections that, if left untreated, may in turn ascend and cause tubal damage. This causal pathway would be supported by the higher incidence of bacterial vaginosis, herpes and other infections in cut women that is documented in the literature (Reisel & Creighton, 2015; RCOG, 2015; Obermeyer, 2005; Morison et al., 2001; De Silva, 1989; Jones, 1999). However, there is little evidence to support an increased susceptibility to STIs specifically (only one study reported on FGM/C and STIs: Elmusharaf, 2006), which can also be a precursor to the development of PID and ensuing TFI.

In the second and third pathways difficulties appears to be due to the injury to the female genitalia that causes narrowing from infibulation (Type III) or the formation of scar tissue (more likely with more extensive cutting). In the second pathway, sexual problems seem plausible because the anatomical changes can make penetration physically difficult, not possible, or painful. In the third pathway obstetric complications also appear to be plausible due to the fact that the anatomical changes could lead to prolonged and difficult labour ultimately resulting in complications such as haemorrhage, foetal complications and emergency C-sections as supported by the literature (Berg & Underland, 2013; Obermeyer, 2005; RCOG, 2015; Reisel & Creighton, 2015; WHO, 2000).

From Figure 3.2.3 it can be seen that the three potential pathways are impacted by the severity of the FGM/C and/or the type of circumciser. In essence what this means is that whether or not FGM/C leads to an infection, sexual problems or obstetric complications is impacted by whether the FGM/C was severe and/or if the circumciser was a lay person. Severe FGM/C (as defined by Type or amount of tissue) potentially increases susceptibility to infection because of the amount of tissue excised or the suturing. Alternatively, the suturing or excessive amount of tissue removed (scar tissue that occurs) involved in the severe forms of FGM/C can lead to difficult or painful intercourse and increase the likelihood of obstetric complications. Infections and reduced or non-existent intercourse would hinder ability to become pregnant, while obstetric complications could lead to having less live births. The effect of infection on fertility seems to be impacted by the outcome of the infection e.g. untreated infection can ascend to the tubes and cause tubal blockage, which would in turn preclude pregnancy, while a treated infection would not have an impact on fertility.

If these propositions are true then the risk of fertility problems would be related to the extent of FGM/C, where women with Type III FGM/C would be at greater risk than Type II,

and they in turn would be at even greater risk than Type I or no FGM/C groups. However, there have not yet been many studies that report on Type III (Obermeyer, 2005) and ones that do often mix Types in analysis (e.g. II and III see Larsen, 2002; I, II and IV see Yount, 2001). It is important to separate the effect of the different types or extents of cutting on fertility problems as a way to disentangle the complex causal mechanisms involved. With regard to infertility some studies have been able to compare different types of FGM/C, such as the study in Egypt comparing women with Type I and II, where women with TFI had higher adjusted odds of having undergone Type II than their fertile counterparts (Inhorn & Buss, 1993).

Reproductive Health Consequences of FGM/C

A summary of the health consequences of FGM/C in the reviewed literature is presented in Table 3.2.2. These five reviews were subjected to quality evaluation using the “Critical Appraisal of Systematic Reviews” published by the WHO (Abalos, Carroli, Mackey & Bergel, 2001). Results of the reviews and quality assessment are briefly described next.

Three of five reviews were systematic in design (Berg & Underland, 2013; Obermeyer, 2005; WHO, 2000) and one reported results of meta-analyses (Berg & Underland, 2013). Search strategies were reported for four of the five reviews (Berg & Underland, 2013; Obermeyer, 2005; RCOG, 2015; WHO, 2000), all four searched major data bases (e.g. Medline, Embase) one searched grey literature (Berg & Underland, 2013) and two searched low resource databases (Berg & Underland, 2013; RCOG, 2015). Four of the five reviews were of high quality, but an evaluation of the quality of one review (Reisel & Creighton, 2015) was not possible because search methodology was not reported.

The reviews included studies that reported on different outcomes that were separated into short and long-term consequences. Consequences can be short-term (occur at the time of

the procedure) or long-term (do not occur immediately following the procedure). Long-term consequences encompass infertility, gynaecological, sexual and obstetric complications. The most serious long-term consequences included labour complications and foetal death, while the most serious short-term consequences reported included haemorrhage and death. Long-term consequences were reported in all five reviews, whereas short-term consequences were reported in only one review (Reisel and Creighton, 2015). Exact figures on the short-term complications were not well documented in the literature and this was attributed to the difficulty obtaining data because of the sensitive nature of the topic (Reisel & Creighton, 2015). Of the long-term outcomes obstetric complications were included in all reviews, while sexual problems, gynaecological infections and infertility were included in three of the five reviews (RCOG, 2015; Reisel and Creighton, 2015; Obermeyer, 2005).

In addition to data from these reviews, in a prospective study the WHO reported on the relative risk of obstetric complications in cut and uncut women in six African countries (Burkina Faso, Ghana, Kenya, Nigeria, Senegal, and Sudan) (WHO study group on female genital mutilation and obstetric outcome, 2006). Results indicated that cut women were significantly more likely to experience harmful obstetric outcomes such as postpartum haemorrhage and stillbirth. The risks appeared to be greater in the more severe forms of cutting, see Table 3.2.2.

Table 3.2.2 summarises the outcomes that were correlated with FGM/C. The percentage of women who experienced complications such as primary and secondary infertility, urinary infections, hepatitis, reduced sexual desire, emergency C-section and still births, was higher in cut than uncut women. Additionally, odds ratios indicated higher likelihood of outcomes such as bacterial vaginosis, herpes, discharge, abdominal pain, genital ulcers and some obstetric complications (most notably post-partum haemorrhage, difficult delivery and pre-labour foetal death) in cut women. Overall it can be concluded that FGM/C

is related to gynaecological consequences such as infections, primary and secondary infertility and some obstetric complications.

Table 3.2.2.

Summary of Reproductive Health Consequences of FGM/C Reported in the Literature

Reproductive outcome	Effect of FGM/C	Statistics reported (where available)		Review
		Percentage	Odds ratio	
Short-term				
	Traumatic bleeding, infection, damage to other adjacent organs, incomplete healing and death	NR		Reisel & Creighton, 2015
Long-term				
Infertility	Childless for more than seven years	2-7 vs 2-6		Obermeyer, 2005
	Primary infertility	1.4-3.3 vs 1.7		
	Secondary infertility	12.7-17.3 vs 15.5		
Gynaecological (Infection)	Bacterial vaginosis		1.7	RCOG, 2015; Obermeyer, 2005; Morison et al., 2001
	Herpes		4.7	
	Urinary infections	11 vs 6		De Silva, 1989; Jones, 1999
	Genital infections		1.7	
	Chronic genital abscesses, vaginal infections, Hepatitis B and HIV	NR		Reisel & Creighton, 2015
	Discharge		1.7-2.8	Obermeyer, 2005
	Genital ulcers		4.4	
	Lesions	7 vs 5		
	Damaged perineum	62 vs 56		
	Cysts	3 vs 2		
Chronic pelvic infection	13 vs 6		El Dareer, 1982; Okonofua, 2002; Obermeyer, 2005	
Abdominal pain		1.5		
	STIs	NR		Elmusharaf, 2006
Sexual	No sexual desire	42 vs 16		Obermeyer, 2005
	no orgasm	43 vs 18		
	Reduced arousal, lubrication, orgasm, satisfaction, sexual quality of life, and dyspareunia and absence of sexual desire	NR		Reisel and Creighton (2015)
Obstetric	Prolonged labour		1.69	WHO, 2000; Reisel & Creighton, 2015; Berg & Underland, 2013
	Obstetric/post-partum haemorrhage (PPH)		2.04	

Reproductive outcome	Effect of FGM/C	Statistics reported (where available)		Review
		Percentage	Odds ratio	
			RR: Type I (1.03), Type II (1.21), Type III (1.69)	WHO, 2006
	Emergency C-section	15.4 vs 6.5		Obermeyer, 2005; Reisel & Creighton, 2015
			RR: Type I (1.03), Type II (1.29), Type III (1.31)	WHO, 2006
	Difficulty in delivery		2.28-2.57	Obermeyer, 2005; Berg & Underland, 2013
	Foetal distress		2.6	WHO, 2000; Obermeyer, 2005
	Still birth	15 vs 11		
			RR: Type I (1.15), Type II (1.32), Type III (1.55)	WHO, 2006
	Pre-labour foetal death		2.5	WHO, 2000; Obermeyer, 2005
	Early neonatal death	NR		
	Obstetric lacerations		1.38	Berg & Underland, 2013
	Instrumental delivery		1.65	
	Pain during and after deinfibulation (anterior episiotomy), maternal death postpartum, postnatal genital wound infection and fistulae formation	NR		WHO, 2000
	Episiotomies and perineal trauma	NR		WHO, 2000; Reisel & Creighton, 2015
	Obstetric complications	NR		RCOG, 2015

Note. NR= data not reported

Table 3.2.2 also summaries results from individual studies on gynaecological infections. Infection that occurs after the initial procedure is labelled as ‘later in life’ to distinguish it from infections that occur at the time of the procedure itself. Studies that demonstrated higher rates of infections in cut women were reported in Table 3.2.2. First, urinary and genital infections were higher in circumcised women, in a sample of Sudanese women in Saudi Arabia (De Silva, 1989). Second, chronic pelvic infection was more

prevalent among infibulated than uncircumcised women in a sample of Sudanese women in five states in Sudan (El Dareer, 1982). Third, in rural Burkina Faso in a study comparing cut and uncut women, genital infection was found to be higher among circumcised than uncircumcised women (Jones, Diop, Askew & Kabore, 1999). Fourth, in Edo State, Nigeria a study comparing circumcised (type unspecified) and uncircumcised women showed higher odds of lower abdominal pain in circumcised women (Okonofua, Larsen, Oronsaye, Snow, & Slinger, 2002). Fifth, in Farafenni, Gambia, women with FGM/C were found to have higher odds of bacterial vaginosis and herpes simplex virus than uncut women (Morison et al., 2001). The majority of these studies did not indicate the type of FGM/C in the sample so conclusions on an association of infection with a specific type or extent of FGM/C could not be drawn.

The increased risk of STI transmission with FGM/C has not been well documented in the literature. However, one study examined the association between STIs and the type of FGM/C/anatomical extent in Sudan (Elmusharaf, Elkhidir, Hoffmann & Almroth, 2006). This was a multi-centred hospital based case-control study on a sample of 222 women. Of the 222 women, 26 tested positive for an STI (gonorrhoeae, chlamydia or Syphilis) and 196 controls tested negative for STIs. The results while non-significant indicated that 85% of women who tested positive for an STI had undergone the severest form of FGM/C (Type III/ labia majora) compared with 78% of controls, and 15% of cases had undergone the milder form involving just the clitoris (Type I) compared with 5.6% of controls. It is important to note that of all 222 women only 3 had not undergone FGM/C while 175 (78.8%) had undergone the most extensive form (Type III). The lack of significance may have been due to the relatively small sample size that would have made it difficult to detect rare complications, the overwhelming number of Type III, or to the lack of an effect, all issues that warrant further investigation in future research. Thus the association

between FGM/C and STIs cannot be confirmed nor denied until unequivocal research is conducted.

It is unclear whether it is the amount of tissue removed or the suturing done that has a pivotal role in the causal pathway to fertility problems, or if there are confounding factors such as the type of circumciser, and education and socio economic status (SES) of the family. One study attempted to disentangle the issue of FGM/C classification by comparing analysis separated by Type (WHO classification) with analysis done by extent of cutting (Almroth, 2005). In this study there were two groups of women, primary infertile women, defined by the authors as younger than 35 and unable to get pregnant after two years of regular unprotected intercourse (n=99) and fertile controls which were pregnant women who had achieved pregnancy in less than two years of regular sexual intercourse (n=179). Analyses were done by comparing the same group of infertile women and fertile controls in two separate analyses, first using WHO classification of FGM/C where the distinction between Type II and III relates to suturing not to the parts excised, and second by comparing the same group of women who have had removal of labia minora versus majora regardless of suturing. The separation of women based on which parts were removed (labia majora, minora) is distinct from the WHO classification (suturing or not) and was done to demonstrate whether it is the parts removed or the suturing that is related to infertility (Almroth, 2005). This distinction can help shed light on the mechanism involved.

Results of the Almroth (2005) study indicated that in the analysis using WHO classification, FGM/C Type III was not significantly associated with infertility (defined as inability to become pregnant after 12 months of unprotected intercourse) whereas in the analysis using anatomical extent of the cutting, FGM/C involving labia majora was significantly associated with infertility. The results indicated that the amount of tissue removed may be more culprit than suturing per se. The amount of tissue removed may

increase the likelihood of infection or scar tissue due to a larger wound at the time of the cutting. Therefore, it may be that infection at the time of the procedure rather than later in life, or difficult intercourse (more likely with suturing) is involved in the causal pathway to fertility problems. Confounding variables such as SES, education, and STIs were included in multivariate analysis and results indicated that these variables did not change the effect size significantly. It is important to note that the difference between WHO classification versus anatomical extent was smaller in the infertile group; Type III (92%), Majora (93%) compared to the fertile control group, Type III (85%), Majora (73%). Therefore, it appears that in the fertile group the severe form (Type III) is overestimated by the WHO classification relative to the anatomical extent classification (Majora). This difference can impact the interpretation of results in the following way: for the infertile group there was hardly any difference between the two classifications (suturing or removal of labia majora) thus inferring which type is related to the infertility can be problematic, whereas in the fertile group there was a difference between the two classifications (smaller percentage involving labia majora than Type III) so it is unclear if this can be interpreted as the fact that the removal of the labia majora is less likely to be connected with infertility than suturing.

In addition to severity of the FGM/C, the type of circumciser has also been suggested to influence the effect of FGM/C on fertility. Inhorn and Buss (1993) examined the effect of type of circumciser (medical professional versus lay person). The results indicated that the adverse effect of Type II FGM/C had a synergistic relationship with having a non-medical circumciser. The issue of traditional practitioners performing the procedure of FGM/C using crude instruments such as knives, razor blades or scissors can impact the likelihood of infection and as indicated previously the majority of circumcisers are traditional practitioners (RCOG, 2015). The lack of use of antiseptics and anaesthetics by traditional practitioners has not been well documented but two articles report a possible link between asepsis and FGM/C

complications but exact figures were not reported (Puri, Kumar & Ramesh, 2011; Inhorn & Buss, 1993).

Rational, Aim and Objectives

It is evident from the literature cited previously that FGM/C has negative consequences on the reproductive health of women, most notably obstetric complications. However, as yet a systematic review for other fertility problems has not been performed. Therefore, the presence of an association between FGM/C and fertility problems, the magnitude of this relationship and the link with type or extent of FGM/C needs to be systematically evaluated. It is important to determine whether reports of fertility problems from FGM/C are due to obstetric complications that lead to fewer live births or to anatomical changes in the female reproductive system (damage to external genitalia or tubes) that lead to an inability to become pregnant.

The biological plausibility of the effect of FGM/C on the reproductive process coupled with the high prevalence in some developing countries and the results of the survey of physicians [FGM/C endorsed as a potential risk factor by 54.2% of responders] (Chapter 2, pp 25), highlighted the need to investigate whether FGM/C should be included as a risk factor in the adapted FertiSTAT. The present study reports on results of a systematic review and meta-analyses of studies on FGM/C. The objective of the review was to examine whether FGM/C was associated with fertility problems in women, the scale of this impact and at what point in the reproductive process FGM/C might exert its impact (ability to achieve a pregnancy or a live birth). The review also intended to identify the presence of an association between fertility problems and the extent or type of FGM/C. The population of interest for the review was women, the exposure was FGM/C (different types) and the outcome of interest was fertility problems. In the present review meta-analyses were performed

according to outcomes available in the included studies and subgroup analyses were planned according to outcomes and type of exposure (FGM/C), to identify whether the effect of FGM/C was on ability to become pregnant or post implantation (ability to have live birth) and if impact was associated with level of exposure. The overall aim of this review was to determine whether FGM/C should be included as a risk factor in the adapted FertiSTAT.

Materials and Methods

Search Strategy

The search terms included words related to FGM/C, for a complete list of MeSH terms see Appendix K. Studies were excluded if FGM/C referred to corrective or feminizing surgery, congenital abnormalities or the acronym FGM/C meant something other than female genital mutilation.

Data Extraction and Quality Assessment

The data extraction form (Appendix H) was adapted to include information relevant to FGM/C. Specifically to include the type of FGM/C, as per WHO classification, see Table 3.2.1 and to include method of ascertainment of FGM/C: self-report, clinical examination or medical/hospital records. The NOS form was adapted to reflect quality criteria for the assessment of FGM/C and additional confounders. FGM/C was adequately assessed if there was independent validation of the degree of cutting as determined by clinical examination or if ascertained from hospital or other medical records. The primary confounder was the type of circumciser.

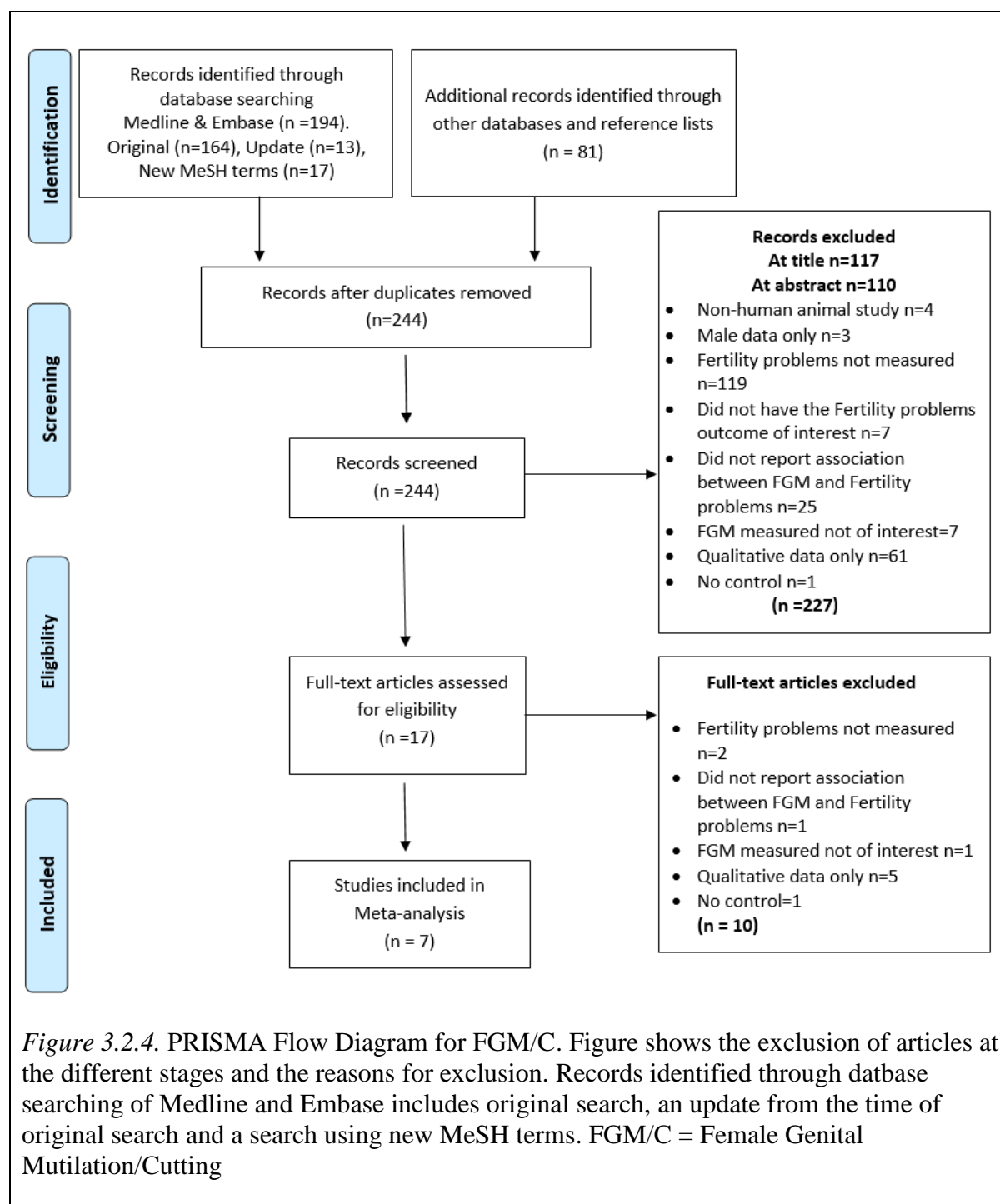
Data Synthesis and Analysis

Meta-analyses were computed separately for the outcomes reported in the studies and where necessary data were calculated as previously described (pp. 65).

Results

Study Selection

Figure 3.2.4 shows the flowchart for number, reason and stage of exclusion of articles. A total of 244 records were identified (after duplicates removed) and most studies (144 of 244, 59.0%) were excluded because they did not report on fertility problems or did not report the relationship between FGM/C and fertility problems. Of the 244 articles 11 were non-English, and sufficient translations were obtained for all using Google translate (<https://translate.google.com/>). Search of the reference lists of the included studies and contact with authors resulted in no additional studies. Of the 17 full text articles assessed for inclusion, seven met inclusion criteria and were included in meta-analyses.



Characteristics and Design of Included Studies

Table 3.2.3 shows selected sample characteristics of the included studies. All of the studies were conducted in Africa and only three included average age at time of study, whereas the other four studies included information related to participant age in range. Table

3.2.4 shows methodological characteristics of included studies. The majority of the studies were cross-sectional design (5 of 7) and two were case-control, see Table 3.2.4. In the cross-sectional studies data was collected from community or household interviews in three studies and from demographic surveys in two. FGM/C was reported as cutting of the female genitalia as classified by the WHO as Type I, II, III or IV in all of the studies. In one study analyses were conducted based on WHO classification as well as ‘anatomical extent regardless of suturing’ (Almroth, 2005). Type III was not included in three of the studies (Inhorn, 1993; Yount, 2006; Klouman, 2005), while two had very low rates (1% and 8.2%), Morison (2001) and Larsen (2000) respectively. Conversely, the two studies from Sudan had very high rates of Type III (85.1% and 87%), Larsen (2002) and Almroth (2005) respectively.

As shown in Table 3.2.4, fertility problems outcome measures in the included studies were: ‘trying-to-conceive for 1 year or more’ in two studies (one of which had a TFI subcategory), ‘trying-to-conceive for 2 years or more’ (TFI only) in one study, ‘unable to become pregnant after 1 year living with partner’ in one study (where primary indicated no pregnancy and no live birth and secondary indicated no pregnancy 1 year after a live birth) and ‘childless after seven-years marriage’ in two studies. One study reported ‘never had live birth after five years’.

Table 3.2.3.

Sample Characteristics Reported in the Seven Included Studies

	Location	Sample (n)	N	N		Age ^a Women	
	Cross-sectional Studies		FGM/C	No-FGM/C (control)		FGM/C	No-FGM/C
Klouman, 2005	Tanzania	969 women	670	299	Mean age (SD)	27 (8)	
Larsen, 2000	Central African Republic, Cote d'Ivoire, and Tanzania	16361 women	6124	10237	NR	NR	NR
Larsen, 2002	Sudan	4218 women	3747	471	NR	NR	NR
Morrison, 2001	Gambia	776 women	420	356	NR	NR	NR
Yount, 2006	Egypt	1729 women	1700	29	Range	Percentage (n)	
					< 25	9.2 (156)	
					25-34	39.1 (664)	
					35-44	34.9 (593)	
					45 +	16.9 (287)	
	Case-control studies		Infertile^b	Fertile (control)		Infertile^b	Fertile
Almroth, 2005	Sudan	279 women	99	180	Mean age (SD)	27.2 (3.9)	24.7 (4.4)
					Range	Percentage (n)	
Inhorn, 1993	Egypt	125 women	39	86	0-19	2.2 (2)	2 (2)
					20-29	41.4 (37)	47 (47)
					30-39	49.5 (44)	40 (40)
					40+	7.1 (6)	11 (11)

Note: ^a Age for women at the beginning of the study; ^b Unable to become pregnant after 12 months of unprotected intercourse; FGM/C=women who have undergone Female Genital Mutilation. SD=Standard deviation NR= data not reported

Table 3.2.4.

Characteristics of the Design of the Seven Included Studies

	Study design	Data collection	Study period	FGM/C assessment	FGM/C self-report or clinical examination	Fertility Problems outcome measure (and duration, where relevant)
Klouman, 2005	Cross-sectional	Community-based survey in rural area	1991-1992	Type I and II	Self-report & Clinical examination	Not able to become pregnant after 1 year living together (primary) Subsequent infertile (secondary) not being able to become pregnant after 1 year from last birth In the analysis combined
Larsen, 2000	Cross-sectional	Demographic and Health Survey (Household interviews)	1995, 1995, 1997	Type I, II and III for Tanzania only. For others only cut v uncut	Self-report	Childless after more than 7 years of marriage, and subsequent infertile defined as still childless 5 years from last birth
Larsen, 2002	Cross-sectional	Demographic and Health Survey (Household interviews)	1989-1990	Type I, II and III	Self-report	Childless after more than 7 years of marriage and subsequent infertile (5 years from last birth)
Morrison, 2001	Cross-sectional	Community based survey in 17 villages (3 tribes)	Jan-July 1999	Type I, II and III	Self-report & Clinical examination	1 year trying to conceive
Yount, 2006	Cross-sectional	Household interviews in rural area	1995-1997	Type I, II and IV	Self-report	Never had live birth after 5 years of marriage
Almroth, 2005	Case-control	Hospital based (urban)	2003-2004	Anatomical extent and Type I, II and III	Clinical examination	2 years trying to become pregnant (TFI subcategory)
Inhorn, 1993	Case-control	Hospital based (urban and rural)	1988-1989	Type I, II and III	Self-report & medical records	1 year trying to become pregnant, (TFI only)

Note. FGM/C = female genital mutilation/cutting; TFI = tubal factor infertility

Study Quality, Fertility Problems Outcome Measure and Bias

Table 3.2.5 shows the results of quality assessment (see table footnote for criteria). The FGM/C group was representative of the population in all studies. FGM/C was adequately assessed (clinical examination) in only three of the seven included studies. The non-FGM/C group (controls) were well defined, selected from the same population and exclusions were adequately reported. Comparability of at least one confounder in the case-control (FGM/C versus non-FGM/C groups) was reported in all of the studies, and four studies reported on ‘circumciser’. Only two of the studies adequately evaluated the included confounders, the majority (5 of 7) used only self-report to assess confounders. Additionally, matching for confounders or including them in analysis was done in three of the studies. Fertility problems outcome was adequately measured in all of the included studies, as indicated by blind or independent assessment. Overall the majority of studies had high or average quality as per quality assessment.

As shown in Table 3.2.6, higher percentages were reported for all outcomes (infertile, childless and TFI) in the exposed (FGM/C all Types or severe Types II and III) group than the none/minimally exposed (No-FGM/C or Type I) group.

Table 3.2.5.

Quality Ratings for the Seven Included Studies on the Basis of an Adapted Newcastle-Ottawa Quality Assessment Scale

Study	Quality Criterion						Overall rating ^g
	Adequacy of FGM/C (exposed) assessment ^a Max 2 points	Adequacy of control (non-exposed), definition and selection ^b Max 2 points	Comparability of control ^c Max 2 points	Confounders adequately assessed Max 2 points ^d	Adequacy of outcome Fertility Problems measure ^e Max 1 point	None response rate or loss to follow-up ^f Max 1 point	
Klouman, 2005	2	2	0	2	1		High
Larsen, 2000	1	2	1	2	1		High
Larsen, 2002	1	2	1	1	1		Average
Morrison, 2001	2	2	1	1	1		High
Yount, 2006	1	2	2	2	1		High
Almroth, 2005	2	2	2	1	1		High
Inhorn, 1993	1	2	2	2	1		High

Note.

^a FGM/C was adequately assessed when independent validation of the degree of cutting was assessed (e.g. clinical examination and/or hospital/medical records) and it was representative of the cohort i.e. drawn from the same population (up to 2 points)

^b Controls were adequately assessed when selection was comparable to cases, and FGM/C was excluded properly in the control population (up to 2 points)

^c Comparability of controls was achieved if exposed/non-exposed were matched or adjustment during analysis conducted. One point for circumciser and one point for any other confounder (up to 2 points)

^d Confounders were adequately assessed if they were obtained from records or a blind interview, and one point was given if the same method was used for both groups (up to 2 points)

^e Fertility problems outcome was adequately assessed if independent or blind assessment was stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.) (up to 1 point)

^f Point given if same rate for both groups and <20% loss to follow up reported

^g The overall quality rating was low (0 to 3 points), average (4 to 6 points), or high (7 to 10 points).

Table 3.2.6.

Number and Percentage of Women with Infertility Childlessness and TFI (n) in the FGM/C and No-FGM/C groups in the included studies (k=7)

Outcomes	Number of women (%)	
	FGM/C	Non-FGM/C
Infertile (>12 months no pregnancy)	117 of 1090 (10.7)	61 of 655 (9.3)
Childlessness	352 of 9903 (35.5)	251 of 7760 (32.3)
TFI (infertile, >12 months no pregnancy)	Type II and III 72 of 276 (26.1)	Non-FGM/C and Type I 15 of 76 (19.7)

Note. FGM/C = Female Genital Mutilation/Cutting; TFI = Tubal Factor Infertility

Results of Meta-analyses

The first meta-analysis compared two studies reporting an ‘infertility >12 months’ (only primary in one study [Morrison, 2001] and primary combined with secondary in the other [Klouman, 2005]). Figure 3.2.5 shows the meta-analysis had non-significant pooled effect (OR 1.17, 95% CI 0.84 to 1.63) and non-significant heterogeneity ($I^2 = 0\%$, $p = 0.54$). The results indicated that the risk of an episode of infertility was not significantly different between the FGM/C and non-FGM/C groups (comparable fertility problems).

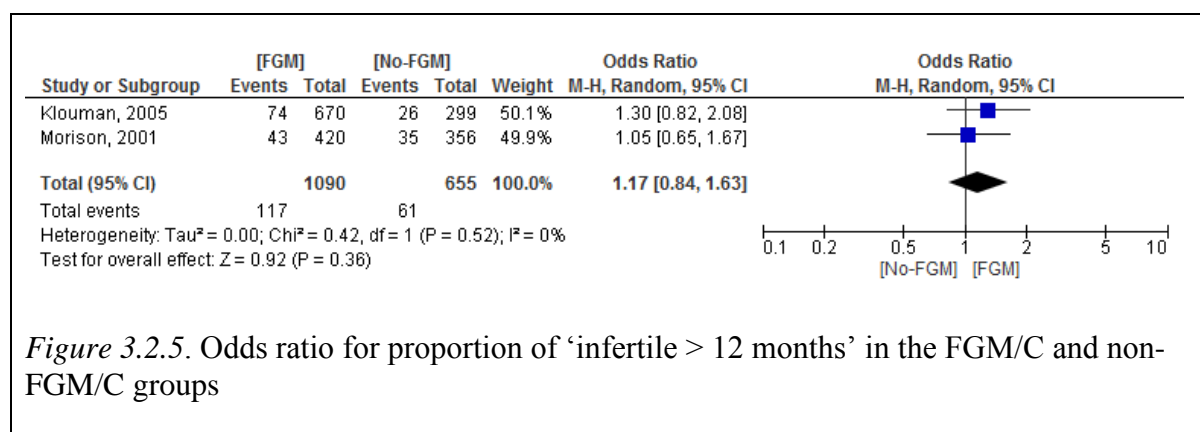
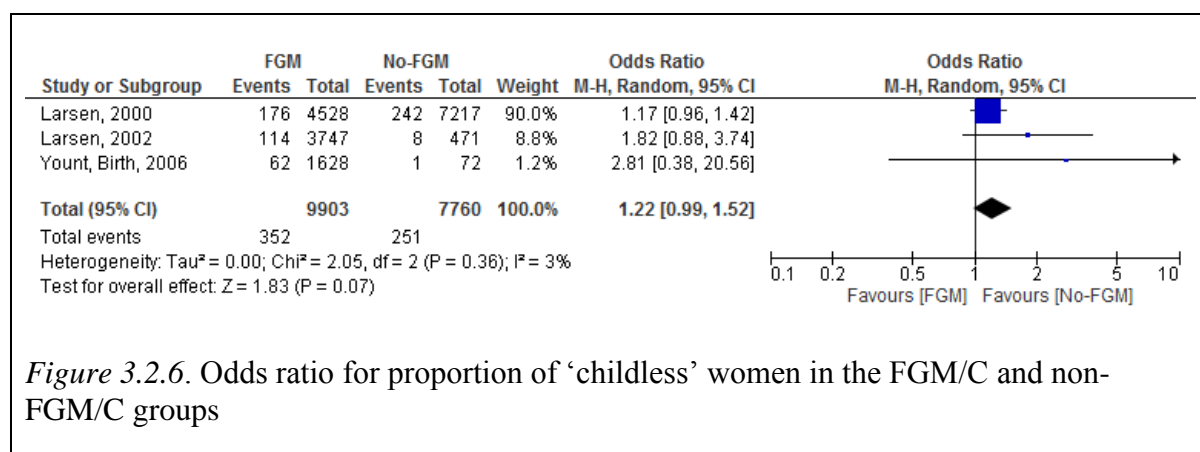


Figure 3.2.6 shows the forest plot and meta-analysis result for the second meta-analysis on the three studies investigating the proportion of ‘childless’ women. The meta-

analysis showed a significant pooled effect size (OR 1.23, 95% CI 1.02 to 1.48), with non-significant heterogeneity between studies ($I^2 = 3\%$, $p = 0.36$). The results indicated that women in the FGM/C group were significantly more likely to be childless (more likely to have fertility problems) than the non-FGM/C group.



The third analysis compared two studies with calculated data representing the proportion of infertile (>12 months) women in the exposed and none or minimally exposed women. Infertility was 12 months in one study and 24 months, and one study included data only on tubal factor infertility (TFI), while the other reported on TFI as well as other aetiologies, thus the meta-analysis only included TFI. In both studies due to the very small number of non-FGM/C participants, the non-FGM/C participants were grouped with Type I as the minimally exposed group. One study reported on all types of FGM/C [but mainly Type III, 85%] (Almroth, 2005), whereas the other only reported on Type I and II (Inhorn, 1993), therefore in the meta-analysis exposure was Type II or III grouped together. Figure 3.2.7 shows this meta-analysis indicated a significant pooled effect size (OR 2.06, 95% CI 1.03 to 4.15), and non-significant heterogeneity ($I^2 = 0\%$, $p = 0.68$). The results indicated that women who had undergone FGM/C Type II and/or III were significantly more likely to have TFI

(more likely to have fertility problems) compared to Type I or no-FGM/C.

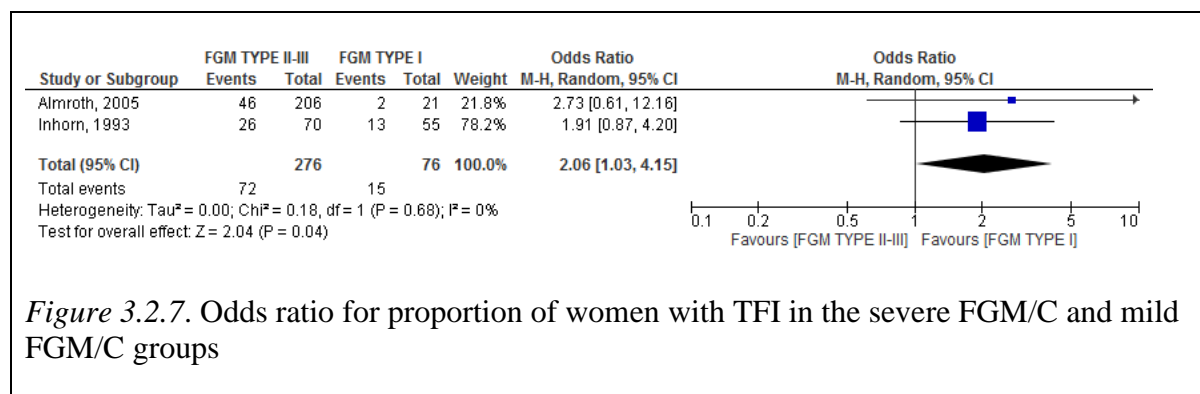


Figure 3.2.7. Odds ratio for proportion of women with TFI in the severe FGM/C and mild FGM/C groups

Subgroup analyses were planned to consider heterogeneity due to outcomes and type of exposure (FGM/C), however, there was no heterogeneity in any of the analyses.

Publication bias assessment.

Publication bias was assessed using funnel plots, Eggers test and trim and fill procedures for one of the analyses (proportion 'childless'), but this was not possible for the other analyses because they comprised too few studies. Egger's tests performed for the meta-analysis was not significant at $P < 0.05$, indicating the lack of publication bias. Trim and fill was used to estimate the number of 'missing' studies and if there were any changes to the magnitude of the pooled effect size if 'missing' studies were included. Figure 3.2.8 shows that the procedure revealed two 'missing' studies in the percentage 'childless' analysis, the pooled effect size changed from (OR 1.22 95% CI 0.99 to 1.52) to (OR 1.17 95% CI 0.98 to 1.4), indicating that inclusion of the two 'missing' studies would have reduced the difference between the FGM/C and non-FGM/C groups but the FGM/C group would still be more infertile than the non-FGM/C group.

however, current results support pathway one. Results of this review suggest that although FGM/C does not decrease the likelihood of pregnancy, severe types (II and III) were found to be associated with TFI and the link between the two would likely be via the mechanism of infection that ascends to the tubes causing TFI. This finding is corroborated by research proposing that FGM/C may be a contributing factor to tubal damage, possibly via increased likelihood of infection (Shandall 1967; Lenzi 1970; Belsey 1979; Reisel & Creighton, 2015; RCOG, 2015). The fact that there was no difference in ability to become pregnant between cut and uncut women in the first analysis (not exclusively TFI) would suggest that if infection is involved it occurs after the women has had a chance to become pregnant (at some point). Therefore, suggesting that post-operative infection occurred later in life (e.g. STIs) rather than at the time of the procedure. Whether the ascending infection was due to the amount of tissue excised or to suturing cannot be determined from this review and should be addressed in future research.

The comparable likelihood of childlessness would suggest that what impact FGM/C has on fertility through TFI does not ultimately render a woman childless. It would also seem that obstetric complications documented in the literature (WHO, 2000; Obermeyer, 2005; Berg & Underland, 2013; Reisel & Creighton, 2015; RCOG, 2015) may not have an effect on childlessness, potentially due to reproductive compensation. Obstetric or perinatal outcomes should be targeted in future investigations of the impact of FGM/C on overall fertility to better understand the third pathway of obstetric complications that can affect the mother and child's health.

Type of FGM/C.

The impact of the specific types of FGM/C on fertility problems was demonstrated by the fact that the severe Type II and III as compared to Type I or no FGM/C were found to be significantly associated with TFI. This supported the hypothesis that the degree of cutting

influences the extent of effects on reproduction (Reisel & Creighton, 2015; WHO, 2000; Obermeyer, 2005; Berg & Underland, 2013). At this time, inferences cannot be made about the difference in impact between Type II and III (effect of suturing) due to the lack of relevant data. It was not possible to identify if amount of tissue removed or suturing is implicated in the causal pathway. Inferences about the effect of type of FGM/C on the other casual mechanism namely, difficult or painful intercourse, could not be made because this consequence is especially profound in the case of infibulation Type III [suturing] (Reisel & Creighton 2015) and data on Type III was limited in the current study. It could be that the impact of FGM/C is only the extent of cutting or only the suturing or an interaction between the two, this can only be determined by an examination of different types separately. Unfortunately the data in this review did not allow one to disentangle this relationship but that should be the goal of future research.

Circumciser.

In addition to the type of FGM/C another factor that may influence the impact of FGM/C on fertility is the type of circumciser who performs the procedure. The RCOG (2015) guidelines indicated that although medicalization of the procedure is increasing it is still largely performed by traditional practitioners in conditions that might not be aseptic. The consideration of type of circumciser was conducted in the majority of primary studies but it was only included in the analysis in two studies. In one of these studies (Inhorn, 1993), the effect of FGM/C on TFI was found to be augmented by having been performed by a traditional circumciser. The inclusion of type of circumciser in a subgroup analysis in the current review was not possible due to insufficient data, thus it should be one of the goals of future research.

In the present study the effect of FGM/C on fertility was examined in a set of meta-analyses of observational studies. Although this systematic approach demonstrated that

FGM/C was not associated with infertility or childlessness, the severe forms of cutting were found to be associated with TFI. However, a causal relationship could not be confirmed, nor could a specific mechanism of action be specified. Therefore, if we apply the ‘Bradford Hill criteria’ noted in the General Methods (pp. 55), we can see that four of the nine apply to the current review and enhance confidence in the causal relationship between FGM/C and fertility problems.

The criterion of ‘specificity’ was met because the association between FGM/C and infertility was only found with a specific type of infertility involving the tubes. This is consistent with the literature (see, Elmusharaf et al., 2006). The criterion of ‘Biological gradient’ was also met because only a specific type of FGM/C, that involving more extensive cutting, was found to be related to infertility consistent with the literature (see, Kraemer et al., 2001). The criterion of ‘temporality’, was met since FGM/C is performed in early childhood before sexual activity and the correlated STIs, PID and tubal damage could have occurred. Finally, the criterion of ‘plausibility’ is met because the model set forth in the literature about how the extent of the cutting can increase likelihood of infection is biologically sound.

Justification for including FGM/C in FertiSTAT.

The current meta-analyses indicated that inclusion of FGM/C in FertiSTAT as a new risk factor was warranted, since knowledge of FGM/C could possibly increase prediction of the inability to become pregnant in women. In the analysis comparing women with severe FGM/C with women with mild or no FGM/C, those with severe type were more likely to have infertility and the infertility was TFI. Therefore, women should be made aware of the potential associated between the severe types of FGM/C and TFI.

Implications of Findings

Results of the current study indicated that FGM/C could potentially improve prediction of fertility problems such as TFI, therefore, awareness of the risks associated with it should be communicated to women. The results of the review cannot support reports in the literature of increased likelihood of obstetric and perinatal complications that may impair maternal and child health because these outcomes were not found in the current search but need to be systematically examined (WHO, 2000; Obermeyer, 2005; Berg & Underland, 2013; Reisel & Creighton, 2015; RCOG, 2015). The implications of these results is that women and health care providers should be made aware of potential risks that women who have undergone Type II and III FGM/C face with regard to increased likelihood of TFI. These results augmented with extant literature can be used to inform women of the adverse effects of FGM/C on childbearing as well as the health risks to mother and child during labour and delivery. The negative impact of FGM/C can be used by anti-FGM/C campaigns that aim to reduce this practice. It is hoped that mothers who are informed of the deleterious impact on their daughters' future health and on their ability to have children will persuade them to stop putting their daughters at risk.

Policy makers and healthcare workers hoping to educate people about the impact of FGM/C on reproductive health can use these results by the implementation of FGM/C care within an inclusive pre-pregnancy care package. The WHO has outlined recommendations about how to address the impact of FGM/C on reproductive health as part of their comprehensive pre-pregnancy care programme (WHO, 2013). Within this package guidelines included; discouraging the practice of FGM/C, screening women to detect complications before pregnancy, educating couples about potential complications, deinfibulation before or during pregnancy to prevent labour complications and treating cysts and other complications

(WHO, 2013). The effectiveness of these interventions should be examined and implemented accordingly where the prevalence of FGM/C is high (e.g., Sudan, Somalia, Egypt).

Due to the large number of migrant populations from countries practicing FGM/C to countries in western nations, health care practitioners in developed countries must also be informed of the potential labour and delivery complications and informed of various aspects of how to prevent maternal and child mortality and morbidity related to FGM/C. FGM/C is already being considered in some countries as evidenced, for example in the UK the RCOG practice guidelines recognise complications of FGM/C (RCOG, 2015). These guidelines include recommendations about training doctors and midwives on the management of FGM/C in gynaecological and obstetric practice e.g. how to carry out gynaecological examination without causing damage, performing deinfibulation before delivery and appropriate suturing after delivery (RCOG, 2015). The guidelines also include information about the legal implications and obligations related to FGM/C for doctors practicing in the UK. Although FGM/C is more prevalent in specific world regions, migrations means it can influence practice in many more countries.

Strength and Limitations in Included Studies

The heterogeneity in study methodology, outcome measures and sample size in included studies could affect the comparability of these studies, and the generalizability of the results of this review. Heterogeneity in FGM/C measure (type and extent), fertility problems outcome (different duration of childlessness, inability to become pregnant), study design (case-control and cross-sectional) and data collection methods (medical examinations and interviews), can affect the practical applicability of the results. However, there was no statistically significant heterogeneity in any of the meta-analyses conducted in this review, indicating that issues of methodological heterogeneity were no longer substantial when

analyses were separated by outcome, study design and duration. The quality of each study independently does not appear to affect the overall results of the review since the majority of studies were of sound quality.

Bias relating to the primary studies included selection bias, information bias and recall bias. In the case-control studies the selection of participants based on hospital attendance can reduce the generalizability of the results. However, because the same sampling procedures were used for both cases and controls, we can assume that selection bias may not be substantial. It can be assumed that since the selection of participants was from the same sample and information was gathered using the same method for both the exposed and non-exposed groups in all the studies, that selection and information bias may not affect results considerably. Recall bias can affect the internal validity of results where data was collected in interviews that require recall of old events, but this is more substantial for recall of details (Hassan, 2005). Thus, recall bias might not have been considerable because the interviews did not require recall of details e.g. period of childlessness or type of FGM/C. The recall or type of FGM/C may not be problematic, however, the identification of type/extent may reduce the reliability of studies that relied solely on self-report, which was the case in four of the seven included studies (Snow, Slinger, Okonofua, Oronsaye, & Wacker, 2002; Klouman, Manongi & Klepp, 2005). Bias due to confounder is a major limitation of the studies included, because matching the groups for confounders or including confounders in the analysis was reported in only three of the included studies. The most important confounder 'circumciser' which may be linked to an increase in the likelihood of infection was only included in the analysis of three studies. There could have been an unequal distribution of other confounders in the exposed and non-exposed groups but this was not reported in the included studies. The effect of confounders like age, age at FGM/C, education

and SES might have influenced the relationship between FGM/C and fertility problems reported in these studies.

Another limitation relating to the primary studies is the use of observational designs, as discussed in the consanguinity review. As in the case of consanguinity randomization would not have been possible or ethical, for FGM/C, therefore the most rigorous design would be cohort studies, followed by case-control and then cross-sectional (Mann, 2003). This study comprised of two case-control and five cross-sectional studies which can be a good starting point to identify associations that can then be followed by more rigorous studies (Mann, 2003), therefore, the results of this review can only be used to infer association.

Future Research

Methodological considerations for research in FGM/C.

Although the negative impact of FGM/C on the health of women and girls has been explored in the literature, the sensitive nature of the topic and the varied ways of defining the different forms of FGM/C may have affected the quality of existing data and evidence (Reisel & Creighton, 2015). In their review, Reisel and Creighton (2015) discussed some of the methodological problems in the field of FGM/C and made recommendations as to how these hurdles can be overcome to produce sound research. Reisel and Creighton recommended that because RCTs were not possible the best research design to study the consequences of FGM/C would be prospective cohort studies. Unfortunately, none of the included studies in this meta-analysis were prospective or retrospective cohort in design (follow over time). The RCOG guidelines (2015) also concluded that research in FGM/C “has been hampered by patchy methodology” (RCOG, 2015, p. 9) as well as the fact that in Africa maternal and perinatal mortality and morbidity are very high due to other variables. Consequently it

becomes difficult to determine the casual role of FGM/C and to state definitively if the FGM/C caused the pregnancy or labour complications.

Obermeyer (2005) reported on the main methodological problems in the field of FGM/C. First, it was noted that while the serious complications may be frequent from a public health perspective, they were statistically rare thus large population-based studies were required to carry out tests of significance. In this review the average sample size across the seven included studies was 3499 (range 190-16,361) with the larger samples in the five demographic studies, and smaller samples in the two case-control studies. Second, many studies used clinic samples that may not be representative of the population because they tend to represent more educated people from high socioeconomic classes. This was not the case in the studies included in this meta-analysis, were the majority of studies were household/community based (5 of 7) and only two were clinical samples, furthermore one of the clinical studies used both urban and rural samples (Inhorn, 1993) while the other used only an urban sample (Almroth, 2005). This would suggest that the overall sample used in the meta-analyses is representative of the population. Third, finding an appropriate control group may be problematic in populations where the prevalence of the practice is very high. This was especially true for studies from Egypt and Sudan, e.g. the two case-control studies had zero to 3% uncut women in the samples (Inhorn, 1993; Almroth, 2005) respectively, while the demographic study in Sudan had 11% uncut women (Larsen, 2002) and the demographic study in Egypt had no uncut women (Yount, 2006). As can be seen from Figure 3.2.2, the rate of uncut women in the populations from which these samples were derived were 12% in Sudan and 9% in Egypt. Thus only the Larsen (2002) study had a rate of uncut women in the study sample representative of the population prevalence. In the other three studies the rate of uncut women was between 31-63%. The rate of the different types of FGM/C also differed from study to study making causal links with type of FGM/C very difficult, e.g. there were no

Type III women in the Inhorn (1993) study and very few Type II (3%) in the Almroth (2005) study. Consequently reducing the ability to make inferences about which Type of FGM/C is related to fertility problems. Fourth, confounders such as ethnicity, education, access to health care and SES should be taken into consideration because these confounders could also explain ill effects of FGM/C. In the current review matching for confounders or including them in analysis was done in three of the studies. In the two case-control studies that considered the relationship between TFI and FGM/C, one included the confounders: age, SES and education in multivariate analysis, all were found not to be significantly associated with TFI (Almroth, 2005) while the other included the type of circumciser (traditional vs medical) and found the traditional circumciser to be significantly associated with TFI (Inhorn, 1993). In the cross-sectional study in Egypt (Yount, 2006) confounders that were included in multivariate analysis were: age, age at marriage, age and procedure, type of circumciser, education, rural-urban, religion and contraceptive use. Results indicated that only religion and contraceptive use were significantly associated with fertility outcomes (never pregnant, childless). These results are not surprising, given that FGM/C practice is predominantly performed by Muslims and contraceptive use reduced the chance of getting pregnant and having live births.

Finally, the issue of exposure to FGM/C and how the extent of the procedure was defined and categorized could affect study quality. Physical examination to ascertain the anatomical extent of the procedure may not always be feasible. Studies that compare self-report and clinical examination seem to show mixed results, and this could be because some women may be able to identify the extent of the FGM/C while others are not (Obermeyer, 2005). Reliance on self-report may further reduce the reliability of studies (Snow, Slanger, Okonofua, Oronsaye, & Wacker, 2002; Klouman, Manongi & Klepp, 2005). In the current review the WHO classification was used in all studies as it is the most widely used

classification system, but one study used WHO classification as well as amount of tissue excised to disentangle the relationships between suturing or tissue excised and TFI (Almorth, 2005). The ascertainment of FGM/C was based on self-report in six of the included studies, and it was augmented with clinical examination in two of those studies (Klouman, 2005; Morison, 2001) but one study used clinical examination only (Almroth, 2005). In the Almroth (2005) study, the clinical examination allowed a comparison of suturing with amount of tissue removed to be analysed, however, since self-report was not used an analysis of discrepancy between clinical and self-report was not possible. In Morison (2001) there was only 3% disagreement between clinical and self-report of Type of FGM/C. While in Klouman (2005) there was 7% disagreement between clinical and self-report of FGM/C, with higher rate of FGM/C being reported by clinical exam than self-report, which may be a reflection of reluctance to self-report rather than an inability to identify it in oneself. The effect of classification on the association with infertility was only performed in one study (Klouman, 2005), where the rate of infertility was higher in the clinically observed group (12.7%) than the self-report group (9.5%). Similar rates of clinical and self-report with minimal discrepancy in the included studies (were such information was available), would suggest that this method of ascertainment has little impact on the results of the current review. On the other hand, issues of classification and their impact on the relationship between FGM/C and fertility problems were only examined in one study (Almroth, 2005). Results of this study indicated that there is indeed a difference in the classification systems; using anatomical extent (parts removed) to operationally define FGM/C was found to be significantly associated with infertility, whereas using WHO classification (amount of suturing) was not (Almroth, 2005). Altogether methodological issues will need to be addressed in future research to produce more robust evidence, as discussed in the next section.

New research.

Future research to disentangle the effect of FGM/C on fertility problems would require RCTs, however, for FGM/C that would be unethical therefore the next best design would be prospective cohort studies to investigate the causal mechanisms that are involved in the different types of FGM/C and which aspects of the reproductive process are affected. It is especially important to investigate the effect of Type II and III separately. Studies should clinically examine the difference between the effect of which parts are removed versus suturing, to understand if the amount of tissue excised renders the women at increased risk of infection and/or scar tissue or if the skinfold caused by suturing leads to more infection and/or difficult penetration. Future research should be directed at understanding the reasons for the lower live birth rate, to definitively ascertain if gestational or perinatal complications are implicated. Finally, it's important to investigate the hypothesis of increased likelihood of infection and reduced intercourse frequency, as well as factors that maybe moderating the effect of FGM/C on fertility problems such as circumcisers, education, age at FGM/C and SES.

Ideally, longitudinal cohort studies following women who have undergone FGM/C and reporting on infections at the time of FGM/C or later in life with follow-up after marriage (reporting on fertility problems outcomes) should be used to help identify if the time of infection is significant. Further, outcomes throughout the reproductive pathway (from occurrence of sexual intercourse to delivery) need to be investigated to build up knowledge of where FGM/C exerts its effects. More research considering women with non-tubal infertility and different types of FGM/C is also required to ascertain if mechanical difficulties are also implicated. Although we have a convergence of results from outcome with duration, the caveat is that the studies from which this information is derived are cross-sectional and few in number. Ideally to study the effect of FGM/C and to understand the biological

mechanisms involved a large population-based prospective cohort study with a sufficiently large control group should be conducted. The study should assess the different types of FGM/C using verification of type of FGM/C with clinical examination/medical records and the distinction between amounts of tissue excised versus suturing. Confounders such as circumciser, age, age at circumcision, ethnicity, education, access to health care and SES should be included by matching the groups or in multivariate analysis. The study should report on outcomes such as infection (at the time of FGM/C and later in life), STIs, HIV, sexual frequency, pregnancy rates, perinatal and obstetric complications as well as live birth rates for the different types of FGM/C.

Conclusion

Fertility problems have been reported as a negative consequence of FGM/C in the literature but evidence to support this claim has been limited. Results of the current meta-analyses indicate that cut women were no more likely to experience infertility or childlessness. However, women with severe cutting (Type II and III) were more likely to be diagnosed with TFI. Therefore, results support the hypothesis that fertility problems increase with the degree of cutting as identified by the WHO classification. In light of the results, inclusion of 'severe FGM/C' as a new risk factor in the adapted FertiSTAT could potentially be justified since it is associated with increased likelihood of TFI. It is important to note that this area of research should be re-examined due to the methodology and the small number of included studies in the meta-analyses.

Study 3.3: Systematic Review and Meta-analysis of Observational Studies Examining the Association of HIV and Fertility Problems

Introduction

The human immunodeficiency virus (HIV) was one of the risk factors identified through the process of adapting the FertiSTAT and was endorsed by the experts in Study 2.1 (Chapter 2, pp. 25). The validity of this risk factor as a predictor of fertility problems was examined in the current systematic review using the operational definitions of fertility problems and risk factor applied in the original development of FertiSTAT (Bunting & Boivin, 2010).

Description of HIV

HIV is a viral infection that impairs the immune system by attacking a type of white blood cell known as CD4 cells (WHO, Case Definitions of HIV, 2007). Once infected with HIV the person's immune system continues to deteriorate leading to immune deficiency. The compromised immune system then renders the body more susceptible to other infections known as opportunistic infections that a healthy immune system is able to fight off. The more advanced stage of the HIV infection is known as Acquired immunodeficiency syndrome (AIDS). A person is said to have AIDS when they have experienced certain cancers, infections, or other severe medical complications (WHO, Case Definitions of HIV, 2007). The most common opportunistic infection and the number one cause of death in HIV infected individuals in Africa is tuberculosis (TB). There are several stages that have been classified for the progression of HIV/AIDS. The WHO classifies the progression of HIV into four stages based on clinical symptomatology, see Table 3.3.1 (WHO, Case Definitions of HIV,

2007). Stage 1 and 2 are milder forms of the disease, whereas 3 and 4 are more severe and are characterized by more infections and marked weight loss known as wasting syndrome (WHO, Case Definitions of HIV, 2007). HIV wasting syndrome is a condition where the individual loses more than 10% of their body weight and the condition does not improve with increased caloric intake; it can be accompanied by diarrhoea and/or fever (WHO, Case Definitions of HIV, 2007). On the other hand, the CDC's classification is based on CD4 count, where category one (lowest severity) is greater than or equal to 500 cells/mL, category two is 200-499 cells/mL and category three is less than 200 cells/mL, category three is also classified as AIDS (Centres for Disease control and Prevention, 2008).

The diagnosis of HIV can be made using various blood tests, usually a combination of antibody testing such as *enzyme immunoassay* (EIA) or *enzyme-linked immunosorbent assay* (ELISA) and confirmation using *Western Blot*, all of which are indirect tests used in the diagnosis of infectious agents by detecting antibodies to these agents (Fearon, 2005). These tests are referred to as indirect tests because they measure the effect of the infectious agent on the immune system rather than the agent itself. Western blot is difficult to perform but produces less false positive results, thus it is used to confirm results of ELISA test. Western blot has been the gold standard in confirming HIV diagnosis since 1989 (CDC and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection, 2014). If the HIV infection is confirmed, the person is said to be HIV positive (HIV+), and if it is not confirmed then the person is said to be HIV negative (HIV-).

At the end of 2014 there were 36.9 million people living with HIV worldwide, with 2.0 million new infections in the year 2014 (The Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015). With 70% of all cases occurring in Sub-Saharan Africa (25.8 million), it is the region with the highest prevalence of HIV globally (UNAIDS, 2015). Sub-Saharan Africa has a reported prevalence of 4.5% of the population infected with HIV, see

Figure 3.2.1. More than half the total number of cases of HIV infection in sub-Saharan Africa are women (UNAIDS, 2015). STIs are reported to be among the risk factors for contracting HIV.

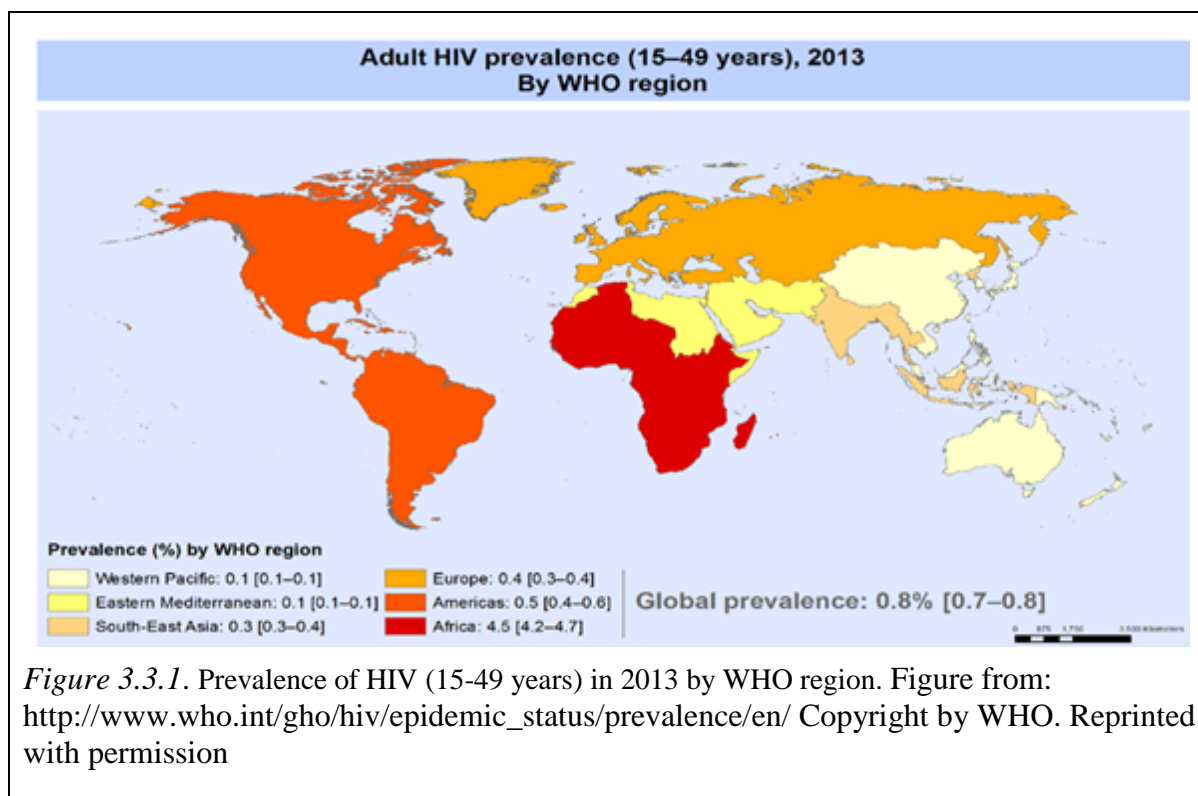
Drug therapy for HIV/AIDS consisted of antiretroviral drugs (ARV) in the late 1980's and more recently (1995-1996) using a combination of at least three ARTs known as highly active antiretroviral therapy (HAART) has been used (Palmisano & Vella, 2011). HAART prevents the virus replicating and can slow the progression of the disease by decreasing the viral load i.e. amount of virus in an infected person's blood (UNAIDS, 2015). The use of HAART has changed the prognosis of HIV from a deadly disease to a chronic manageable disease (UNAIDS, 2015).

Table 3.3.1.

WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

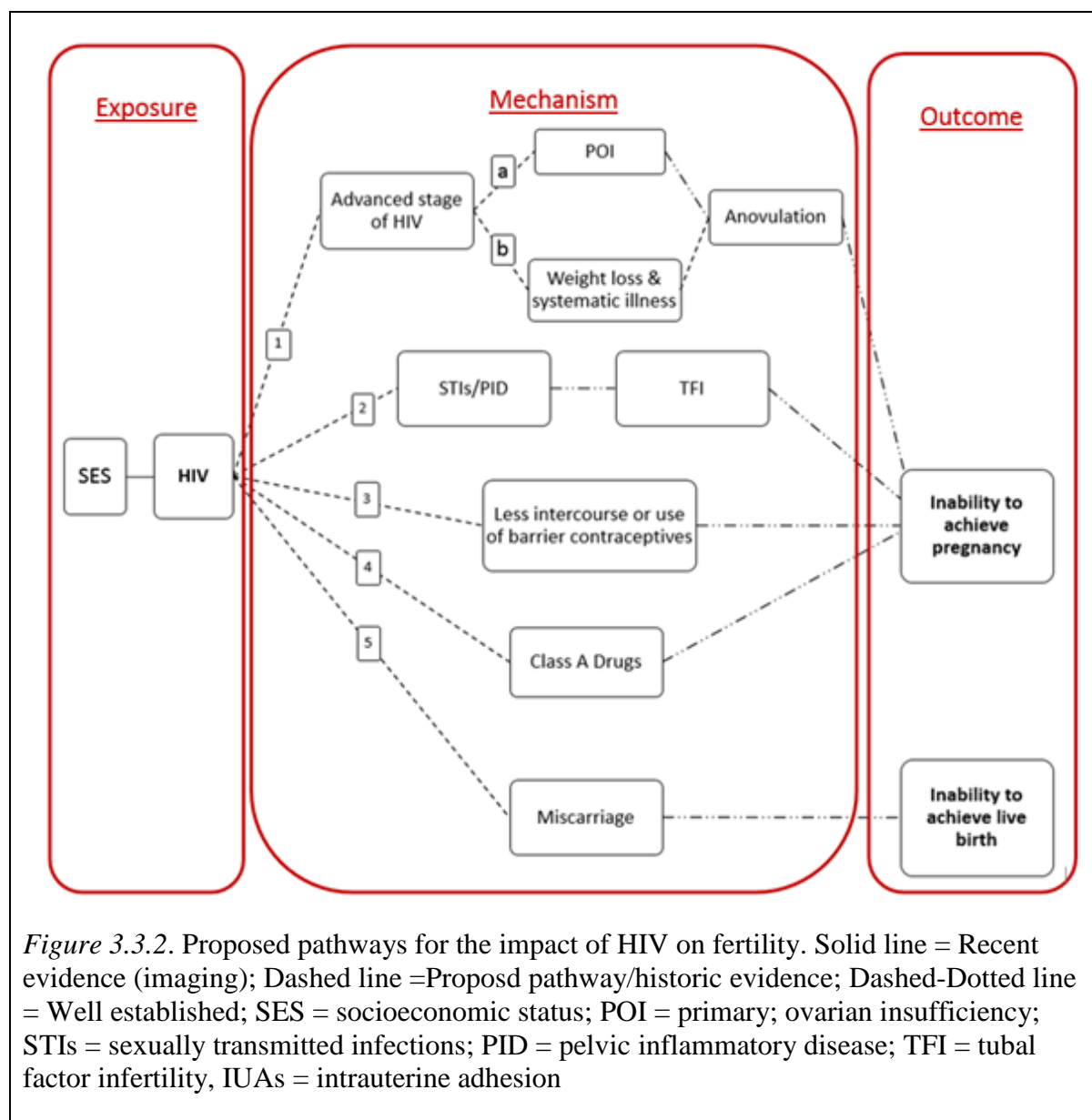
Clinical Stage	Clinical Conditions or Symptoms
Primary HIV Infection	Asymptomatic Acute retroviral syndrome
Clinical Stage 1	Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2	Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent infections (respiratory, Herpes, oral ulceration, Seborrhic dermatitis Fungal nail infections)
Clinical Stage 3	Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for >1 month Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant) Persistent oral candidiasis (thrush), Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Unexplained anemia (hemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/μL) Chronic thrombocytopenia (platelets <50,000 cells/μL)
Clinical Stage 4	HIV wasting syndrome Recurrent infections (severe bacterial pneumonia, Chronic herpes, Esophagea candidiasis, Extrapulmonary tuberculosis, Cytomegalovirus infection) Cancer (Kaposi sarcoma, Lymphoma, Invasive cervical carcinoma) Central nervous system toxoplasmosis Other severe infections and cancers

Note. Table adapted from Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2nd edition. WHO, 2016. <https://www.ncbi.nlm.nih.gov/books/NBK374293/> Copyright by WHO [2016]. Reprinted by permission.



Plausible Mechanisms to Explain why HIV Could be Associated with Fertility Problems

Evidence from the literature suggests that the causal mechanism involved in the effect of HIV on fertility may be a multifactorial chain of events. There are potential factors that affect the impact of HIV on fertility in general, including age, weight loss (wasting), systemic illness, stage of disease, STIs, a history of intravenous drug use and other substance abuse as well as sociodemographic factors (Lo & Schambelan 2001; Kushnir & Lewis, 2011). However, the exact biological pathway for the effect of HIV infection on reproductive outcomes may be difficult to uncover for several reasons, one such reason is that being diagnosed with HIV may be followed by a decline in sexual activity (Lo & Schambelan 2001). Based on the information obtained from the literature a model was constructed to depict the potential casual pathways, see Figure 3.3.2.



As can be seen in Figure 3.3.2, anovulation (not ovulating) is a factor in two of the pathways, the first is via weight loss and/or systemic illness and the second via of primary ovarian insufficiency (POI). The stage of disease is a precursor for weight loss/systemic illness and POI. Although, hormonal dysfunction (endocrinological and/or ovarian) has been indicated in several reviews (Waters, et al., 2007; Kushnir & Lewis, 2011), a direct inhibitory effect of HIV on ovarian function has not been supported. However, POI has been implicated

as a factor in the potential pathway for the impact of HIV on fertility in several studies (Kushnir & Lewis, 2011). Menstrual irregularities and amenorrhea may be a direct result of ovarian dysfunction or result as a consequence of complications/comorbidities of HIV (e.g., weight loss). Factors that have been described to be associated with menstrual irregularities reported in HIV (without wasting) include; drug abuse, marijuana, chronic alcohol consumption, low SES (Lo & Schambelan 2001), low CD4 count and high HIV viral load (Waters, et al., 2007).

POI is a condition that affects about 1% of women and is characterised by premature menopause, i.e. before the age of 40, compared to 51 for normal menopause (Cox & Liu, 2014). When a women's hormones change prematurely to resemble those of menopause, regardless of the etiology of the change a diagnosis of POI is made. POI has been used to encompass several hormonal disorders including premature ovarian failure (POF), hypergonadotropic hypogonadism and ovarian dysgenesis, and is thus used to describe compromised ovarian function on a continuum rather than a specific endpoint (Cox & Liu, 2014). The diagnosis of POI can be confirmed by detecting follicle-stimulating hormone (FSH) levels greater than 30U/L in the presence of amenorrhea for 4-6 months (Cox & Liu, 2014). In the 2015 European Society of Human Reproduction and Embryology (ESHRE) guidelines for the management of POI, it was concluded that FSH is the gold standard for diagnosis of POI, however there hasn't been consensus as to an exact cut-off (ESHRE, 2015). Cut-offs include 25, 30, 40 and 50, but the etiology of POI contributes to the level of FSH, where women with autoimmune causes have been found to have lower levels of FSH while women with idiopathic POI had higher levels. Therefore, the ESHRE guidelines state that a cut off level of FSH > 25 IU/l would be more inclusive. More recently anti-Mullerian hormone (AMH) has been used as a marker for POI (La Marca, et al., 2006), however women with regular cycles and low ovarian reserve may also have low AMH, thus on its own AMH

should not be used to diagnose POI (ESHRE, 2015). Decreased ovulation or anovulation occurs in POI due to a congenital decline in follicles, accelerated follicular degeneration or an inability to recruit follicles (Nelson, 2009), whereas in menopause there is permanent cessation of menses due to the complete depletion of follicles. In contrast to menopause it is reported that 50% of patients with POI will have varying degrees of ovarian function and that 5-10% are able to achieve unassisted conception (Cox & Liu, 2014; Nelson, 2009).

The second pathway in Figure 3.3.2, depicted the suspected increased susceptibility to STIs and severity of pelvic infections (Kushnir & Lewis, 2011; Lo & Schambelan 2001; Waters, et al., 2007). In the third pathway, reduced penetrative sexual intercourse and/or use of barrier contraceptives e.g. condoms can potentially explain how HIV affects fertility (Lo & Schambelan 2001; Kushnir & Lewis, 2011). In the fourth pathway, class A drugs have been depicted because the use of class A drugs is correlated with HIV and class A drugs have a proven independent impact on fertility (Mueller et al., 1990; Hassan & Killick, 2004). In the final pathway, increased miscarriage is depicted as a factor that could lead to reduced ability to have live birth (Kushnir & Lewis, 2011).

Reproductive Health Consequences of HIV

The negative impact of HIV on women's reproductive health and specifically fertility problems has been explored in the literature over the past few decades. A summary of the consequences in the reviewed literature is presented in Table 3.3.2, and these will be discussed next. The four reviews summarized were subjected to quality evaluation using the "Critical Appraisal of Systematic Reviews" published by the WHO (Abalos, Carroli, Mackey & Bergel, 2001).

Specific figures for prevalence of health consequences were not reported in all of the reviews. In a commentary about research on reproductive function and HIV, Lo and

Schambelan (2001), discussed ovarian function as well as other markers of fertility in HIV infected women. In a narrative review of the literature on HIV and subfertility, Waters, Gilling-Smith and Boag (2007) conducted a search of PubMed, however, no details on search methodology were reported to allow adequate quality assessment of the review. The results of the review indicated that some studies have shown an association between HIV and fertility problems. In another narrative review of the literature on the impact of HIV on fertility problems PubMed was searched, but search methodology and exact figures were not reported (van Leeuwen, et. al., 2007). Results of this review indicated that HIV can be detected in the female reproductive tract, however, evidence for the impact of HIV on reproduction was inconsistent. Most of the studies cited in this review were conducted in Africa and may not be generalizable to other populations (van Leeuwen et. al., 2007). In a more recent systematic review and meta-analysis on HIV and infertility, Kushnir and Lewis (2011), conducted a search on PubMed for studies pertaining to how subfertility is affected by HIV infection, comorbidities (e.g. STIs, drug use) and HIV drug treatment (antiretroviral therapy).

Overall the reviews included 24 primary studies with each review mainly updating new primary studies. However, the two most recent reviews (van Leeuwen et al. 2007; Kushnir & Lewis, 2011) included several studies that were published prior to the previous reviews suggesting different search methodologies and/or inclusion criteria may have been used.

The summary of evidence presented in Table 3.3.2 suggests that HIV has been found to be associated with reproductive functioning, but results were inconsistent across the literature. For effects on ovarian reserve, the evidence was mixed, with some studies reporting an association between HIV and reduced ovarian function (including elevated FSH levels), and other studies reporting no difference. Similarly, with regards to amenorrhea the evidence was mixed with some studies reporting an association with HIV while others

reporting no such association. With regard to menstrual irregularities, the majority of evidence pointed to an association between HIV and menstrual irregularities that in some studies was shown to be related to stage of disease. Regarding the other outcomes (comorbid STIs, tubal blockage, reduced pregnancy and birth rates and increased abortion/miscarriage), all the cited evidence indicated an association with HIV.

Table 3.3.2.

Summary of Reproductive Health Consequences of HIV Reported in the Literature

Reproductive outcome	Effect of HIV	Primary study	Statistics reported (where available)	Review
Ovarian function	Change in ovarian reserve in HIV+ women Mixed results	Schoenbaum et al. (2005); Martinet et al. (2006) reported normal ovarian reserve	NR	van Leeuwen et al. (2007)
		Clark et al. (2001); Englert et al. (2004) reported dramatically reduced ovarian function i.e. Primary ovarian insufficiency (POI)	NR	
	FSH level	Clark et al. (2001) report higher rates of elevated FSH	8% of HIV+ women (20-42yrs) had FSH level indicative of menopause	Kushnir and Lewis (2011)
		Cejtin et al. (2006) reported no difference in FSH in women with amenorrhea Seifer et al. (2007) found no evidence that HIV infection influences ovarian aging (FSH and AMH levels)	NR	Kushnir and Lewis (2011)
Ovaries susceptible to HIV and secondary infections	Not well studied but hypothetically i.e. no specific evidence	NR	Lo and Schambelan (2001)	
Menstrual cycle	Menstrual irregularities (very short and very long) in HIV+ women without AIDS	Chirgwin et al. (1996)	NR	van Leeuwen et al. (2007); Lo and Schambelan (2001); Waters et al. (2007)
	Increased rate of menstrual irregularities in HIV infected women with AIDS (and the associated wasting).	Harlow et al. (2000)	NR	van Leeuwen et al. (2007)
		Grinspoon et al. (1997)	NR	Lo and Schambelan (2001)
HIV+ had little effect on menstrual irregularities (cycle)	Harlow et al. (2000)	NR	Lo and Schambelan (2001);	

Reproductive outcome	Effect of HIV	Primary study	Statistics reported (where available)	Review
	length/ menstrual duration)	Harlow et al. (2000); Chirgwin et al. (1996)	NR	Waters et al. (2007) Waters, et al. (2007); van Leeuwen et al. (2007)
	Among HIV+ women, increased cycle variability was associated with higher viral loads and lower CD4 cell counts	Harlow et al. (2000) Clark et al. (2001)	NR NR	Lo and Schambelan (2001); Waters et al. (2007) Waters et al. (2007)
Amenorrhea	Prolonged amenorrhea without ovarian failure	Cejtin et al. (2006)	HIV+ women 3 times more likely to have prolonged amenorrhea without ovarian failure	Kushnir and Lewis (2011)
	Increased rate of amenorrhea	Chirgwin et al. (1996)	NR	Lo and Schambelan (2001); Kushnir and Lewis (2011); Waters et al. (2007)
	Being HIV+ had little overall impact on amenorrhea	Harlow et al. (2000) Ellerbrock et al. (2007); Harlow et al. (2000)	NR NR	Lo and Schambelan (2001); Waters et al. (2007) Kushnir and Lewis (2011)
Comorbid STIs	A high incidence of comorbid STIs in HIV+	Paxton et al. (1998); Gray et al. (1998); Wawer et al. (1998) Frankel et al. (1997); Sobel (2000)	NR NR	Kushnir and Lewis (2011) van Leeuwen et al. (2007)
Tubal blockage	Higher rates of tubal blockage Higher STIs suggesting that women who are HIV+ may be at increased risk of tubal damage. Tubal occlusion	Frodsham et al. (2006) Frankel et al. (1997); Sobel (2000) Coll et al. (2007)	NR NR 27.8% among HIV+ women	Waters et al. (2007) van Leeuwen et al. (2007) Kushnir and Lewis (2011)
Pregnancy rate	Lower pregnancy rate in HIV+ women	Zaba et al. (1998) [Africa]	fertility was 25% to 40% lower in HIV+	Kushnir and Lewis (2011)

Reproductive outcome	Effect of HIV	Primary study	Statistics reported (where available)	Review
		Massad et al. (2004) [USA]	women in Sub-Saharan Africa NR	
		Stephenson et al. (1996); Thackway et al. (1997); De Vincenzi et al. (1997)	NR	Lo and Schambelan (2001)
		Zaba and Gregson (1998) (Regardless of STIs)	NR	van Leeuwen et al. (2007)
	Dramatic decline in pregnancy rate in HIV+ women with increased progression of the disease	Sedgh et al. (2005)	NR	van Leeuwen et al. (2007)
Birth rate	Lower birth rate in HIV+ women	Stephenson et al. (1996); Thackway et al. (1997); De Vincenzi et al. (1997)	NR	Lo and Schambelan (2001)
Abortions/miscarriage	Pregnancy loss was more common among HIV+ women	Gray et al. (1998)	HIV+ vs. HIV- (18.5% vs.12.2%)	Kushnir and Lewis (2011)
	Before HAART pregnancy loss was much more common among HIV+ women	D'Ulbaldo et al. (1998)	67% higher among HIV+	Kushnir and Lewis (2011)
	Miscarriage rate remained constant from 1990 through 2006 despite evolution of therapy during this period	Townsend et al. (2008)	Miscarriage rate of 4%	Kushnir and Lewis (2011)
	Higher rates of abortion	Stephenson et al. (1996); Thackway et al. (1997); De Vincenzi et al. (1997)	NR	Lo and Schambelan (2001)

Note. NR = not reported; POI = Primary Ovarian Insufficiency; FSH = Follicle-Stimulating Hormone; AMH = Antimullerian hormone; CD4 = Type of white blood cell; STIs = Sexually Transmitted Infections; PID = Pelvic Inflammatory Disease

In addition to the aforementioned reviews, there have been several studies that reported a reduced pregnancy rate in HIV+ women, without mention of period of exposure to risk of pregnancy (Ryder et al., 2000; Ross et al., 1999; Ross et al., 2003; Sedgh et al., 2006; Glynn, 2000). These studies can be used to demonstrate a possible association between HIV and reduced prevalence of pregnancy, but they cannot be used to ascertain the effect of HIV on rate of infertility (because that would require knowing that the period of exposure to pregnancy was more than one year). The lack of information about the period of exposure to

pregnancy precluded the inclusion of these studies in the current meta-analysis and may be the reason why these studies were not included in the abovementioned reviews.

In a cohort of Ugandan women attending routinely at a rural AIDS clinic over a seven-year period it was found that pregnancy rate was 7% in HIV+ women and 9.5% in HIV- women (Ross et al., 1999). However the duration of exposure to the risk of pregnancy was not reported and a proportion of the women in the study (13% of HIV+) and (18% of HIV-) had no sexual partners in the last year. In the same cohort of women followed over a longer period of time (11 years), reduced pregnancy rate with increased stage of disease (10.9% in HIV-, 8.5% in stage 1, 7% in stage 2, 5% in stage 3 and 1.1% in stage 4) was reported (Ross et al., 2003). These results suggest that the severity of the disease (stage) impacts on ability to become pregnant, which may be related to the systematic illness and weight loss that become more pronounced with progressive stages of the disease. A study comparing pregnancy rate in serodiscordant couples in the Democratic Republic of the Congo, found that pregnancy rate was lower in couples where the women was HIV+ (11.6%) than in couples where the woman was HIV- (15%), but there was no control group where both partners were HIV- (Ryder et al., 2000).

There have been various studies that measured the prevalence of HIV in infertile populations including a study on stored frozen sera in a tertiary care center in the USA that found the prevalence of HIV to be 0.6% of women in a low-middle class infertile population (Bray, Soltes, Clarke, Minkoff, Sierra & Reyes, 1991). In another prevalence study among Spanish patients attending an infertility clinic in Barcelona, prevalence of HIV was found to be 0.3% in primary infertile women and spontaneous recurrent aborters (Balasch, Pumarola, Jove, Coll & Vanrell, 1991). In a community survey in Gabon in the late 80s on prevalence of HIV in infertile women (primary and secondary) and fertile controls, it was found that 9.3% of primary infertile (childless for more than two years), 2.1% of secondary infertile

(childless for more than two years following the last birth) and 0.7% of fertile controls were HIV+ (Schrijvers, 1991).

Rational, Aim and Objectives

The studies mentioned thus far indicate that HIV impacts negatively on aspects of female reproductive health, most notably amenorrhea, menstrual irregularities, decreased pregnancy rate and increased pregnancy loss (Waters, et al., 2007; van Leeuwen et. al., 2007; Kushnir & Lewis, 2011; Ryder et al., 2000; Ross et al., 1999; Ross et al., 2003, Schrijvers, 1991). The negative impact of HIV on fertility problems has been suggested but there is a lack of unequivocal evidence to support this suggestion. The presence of an association between HIV and fertility problems, the magnitude of this relationship and the link with stage of HIV or CD4 count need to be explored. It is important to understand whether reports of fertility problems are due to hormonal changes (directly caused by HIV or indirectly by other factors such as weight loss), anatomical changes in the female reproductive system (damage to tubes) or behavioural changes (abstinence or use of condoms during penetrative sex) that could lead to difficulty becoming pregnant. It is unclear whether it is the HIV virus itself or the decreased immune response and ensuing increased susceptibility to opportunistic infections that impacts on fertility problems or if there are confounding factors such as age, STIs, stage of HIV, contraceptive use, education and SES.

The biological plausibility of the effect of HIV on reproductive processes coupled with the high prevalence in some developing countries and the results of the survey of physicians [HIV endorsed as a potential risk factor by 75.9% of responders] (Chapter 2, pp 25), highlights the need to investigate whether HIV should be included as a risk factor in the adapted FertiSTAT. The review also intended to examine hormonal changes and amenorrhea as plausible biological pathways. The present study reported on results of a systematic review

and meta-analyses of studies on HIV. The objective of the review was to examine whether HIV was associated with fertility problems in women, the scale of this impact and at what point in the reproductive process HIV might exert its impact (ability to become pregnant or have a live birth). The population of interest for the review was women, the exposure was HIV (seropositive) and the outcome of interest was fertility problems. The overall aim of this review was to determine whether HIV should be included as a risk factor in the adapted FertiSTAT.

Materials and Methods

Search Strategy

The search terms included words related to HIV, for a complete list of MeSH terms see Appendix L. Studies were excluded if the acronyms HIV or AIDS referred to or meant something else. Due to the extensive amount of literature on HIV not relevant to this review the search was modified by only including some subject headings and by excluding studies using the 'NOT' Boolean to remove studies on topics such as cancer and ethics, see Appendix L for the complete search strategy. For the search term AIDS only the following subheadings were included: *complications, diagnosis, disease management, drug resistance, drug therapy, epidemiology, etiology, radio therapy, rehabilitation and side-effects*.

Data Extraction and Quality Assessment

The data extraction form (Appendix H) was adapted to include information relevant to HIV. Specifically to include stage of HIV and type of blood testing used for the diagnosis of HIV in included studies. The NOS form was adapted to reflect quality criteria for the assessment of HIV and additional confounders. HIV was adequately assessed if there was

blood testing using ELISA and/or Western Blot during clinical examination or from hospital/medical records. The confounder that was more important than others was age.

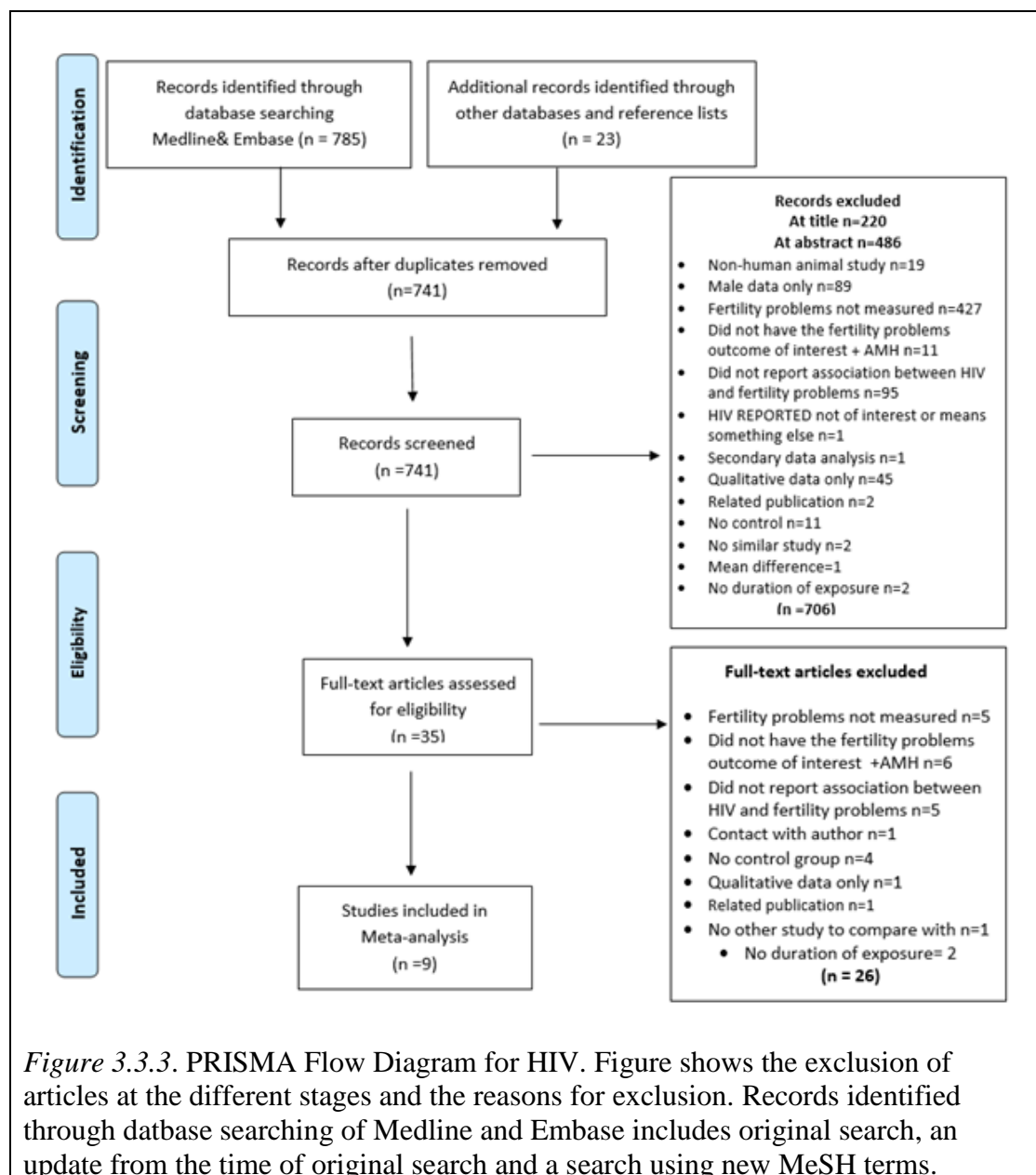
Data Synthesis and Analysis

Meta-analyses were computed for the outcomes reported in the studies. Data from case-control studies were calculated as previously described (pp. 65)

Results

Study Selection

Figure 3.3.3 shows the flowchart for number, reason and stage of exclusion of articles. A total of 741 records were identified (after duplicates removed) and most studies (522/741, 70.4%) were excluded because they did not measure fertility problems or report the relationship between HIV and fertility problems. Three studies were non-English, and translations were obtained using Goggle translate (<https://translate.google.com/>). Search of the reference lists of the included studies and contact with authors resulted in 2 additional studies. Of the 35 full text articles assessed for inclusion, nine met inclusion criteria.



Characteristics and Design of Included Studies

Table 3.3.3 shows selected sample characteristics of the included studies. The majority of the studies were conducted in Africa (7/10, 70%) and six included mean or median age at time of study, two studies included information related to participant age in range and two did not report on age. The average age in the HIV+ group (of studies that reported mean or median) was 28.9 (range 16.7-35) and in the HIV- group was 28.12 (range 16.9-34.5).

Table 3.3.3.

Sample Characteristics Reported in the Ten Included Studies

Study	Location	Sample (n)	N		Age ^a Women		
			HIV	No-HIV	HIV	No-HIV	No-HIV
Cohort/cross-sectional studies							
Cejtin, 2006	USA	1431 women	1145 women	286 women	Range	Percentage (n)	Percentage (n)
					16–39	59.1 (677)	63.6 (182)
					40–44	25.2 (288)	25.5 (73)
					45–49	11.4 (131)	8 (23)
					50–55	4.3 (49)	2.8 (8)
Chirgwin, 1996	USA	330 women	248 women	82 women	Mean (SD)	32.7 (6.2)	34.5 (6.9)
Gray, 1998	Uganda	4497 women	953 women	3544 women	Range	Percentage (n)	Percentage (n)
					15–19	23.9 (847)	7.1 (68)
					20–24	26.5 (938)	30.7 (293)
					25–29	16.3 (578)	30.6 (292)
					30–39	21.9 (775)	26.1 (249)
					>40	11.5 (406)	5.4 (51)
Linan, 2011	USA	1412 women	941 women	471 women	NR	NR	NR
Willems, 2013	Burkina Faso	93 women	54 women	39 women	Mean (SD)	35 (5)	29 (6.5)
Ross 2003	Uganda	216 women	81 women	135 women	NR	NR	NR
Yaro 2001	Burkina Faso	912 women	63 women	849 women	Mean (SD)	16.7 ±2	16.9±2
Ezechi 2010	Markurdi, Nigeria	3473 women	2549 women	924 women	Mean age	32.7± 4.9	33.2±5.7
Case-control studies							
			Infertile^b	Fertile (control)		Infertile	Fertile
De Muylder, 1990	Zimbabwe	331 women	227	104	Mean (SD)	28.4 (4.8) tubal 27.1 (4.9) non-tubal	NR
Dhont, 2010	Rwanda	595 women	312	283	Median (IQR)	30 (27–35)	27 (24–31)

Note. ^a Age for women at the beginning of the study; ^b Unable to become pregnant after at least 12 months of unprotected intercourse; NR= data not reported; SD=Standard deviation; IQR=inter-quartile range

Table 3.3.4 shows methodological characteristics of included studies. Two studies were cohort design, information extracted in three studies was cross-sectional data embedded within a larger cohort study, two studies were cross-sectional and two were case-control. HIV was confirmed by a blood test in all of the studies (specified as ELISA and/or Western blot in half of the studies).

Fertility problems outcome measures reported in the included studies were: ‘pregnancy rate’ (calculated no-pregnancy) in two studies, ‘FSH level only’ in one study, ‘amenorrhea only’ in one study, ‘FSH and amenorrhea’ in one study, ‘infertility >12 months’ in two studies (more than 12 months unprotected sex in one study and more than 18 in the other study). The two studies that reported ‘pregnancy rate’ reported levels of contraceptive use as follows; 84% of HIV+ and 79% of HIV- women used a contraceptive in the 6 months prior to the study (Linas, et al., 2011), while 14.3% of HIV+ and 10.7% of HIV- women used modern contraceptives and 6.7% of HIV+ and 5.7% of HIV- women used abstinence (Gray, et al., 1998). The Gray et al. (1998) study was a prospective cohort study reporting on pregnancy rate in HIV+ and HIV-. Pregnancy was determined at the beginning of the study at baseline and all the women who were not pregnant were followed over time to measure pregnancy rate but the final pregnancy rate was not given per woman rather it was given in women years, so it was not possible to use the prospective data in the current meta-analysis. Instead the baseline data regarding the number of women who were pregnant and those who were not pregnant in both the HIV+ and HIV- groups at the beginning of the study was extracted and used in the current meta-analysis (thus it was cross-sectional because it was obtained at one point in time). The data in Linas et al. (2011) on the other hand was prospective cohort since these women were followed over a 7-year period. In this study 766 pregnancies occurred in 456 women, meaning some women had more than one pregnancy in the seven year period, therefore the number of women who became pregnant (456) was used

Table 3.3.4.

Characteristics of the Design of the Ten Included Studies

Study	Study design	Data collection	Study period	HIV self-report or Blood test	Fertility Problems outcome measure (duration)
Cejtin, 2006	Cross-sectional data embedded in a Cohort study	Interagency HIV Study Hospital/clinic based	1994-1997	Blood test (type not specified)	Amenorrhea > 12 months And/or FSH > 25 (mUI/ml)
Chirgwin, 1996	Cross-sectional data embedded in a Cohort study	Hospital/clinic based	1991-1994	Blood test (type not specified)	Amenorrhea > 3 months
Gray, 1998	Cross-sectional data embedded in a Cohort study	Community based	1994-1995	Blood test (Western-blot)	Pregnancy rate per woman (we converted to no-pregnancy)
Linas, 2011	Cohort	Interagency HIV Study Hospital/clinic based	2002-2009	Blood test (HIV RNA, CD4 count and Serology)	Pregnancy rate per woman (we converted to no-pregnancy)
Willems, 2013	Cross-sectional data	Hospital/clinic based	2008	Blood test (ELISA and Western-blot)	FSH > 40 (mUI/ml)
De Muylder, 1990	Case-control	Hospital based	1985-1987	Blood test (ELISA and Western-blot)	More than 18 months unprotected sex
Dhont, 2010	Case-control	Hospital based & community	2007-2009	Blood test (Rapid test)	More than 12 months unprotected sex
Ross 2003	Cohort study	Clinic based	1990-2001	Records (CD4 count & WHO staging)	Foetal loss- spontaneous abortion and still birth
Yaro 2001	Cross-sectional	Clinic based	1988	Blood test (type not specified)	Live birth, still birth, abortion
Ezechi 2010	Cross-sectional	Research institute & medical centre	2005-2007	Blood test (ELISA, Western bolt, CD4 count and viral load)	Amenorrhoea > 90 days

Note. HIV = Human Immunodeficiency Virus; CD4 = cluster of differentiation 4; RNA = Ribonucleic Acid ; FSH = Follicle Stimulating Hormone; ELISA = Enzyme-linked Immunosorbent Assay

in the meta-analysis. Additionally, there were problems with the contraceptive use data e.g. of the 766 reported pregnancies, 192 occurred at the same visit that hormonal contraception use was also reported by women, but it was unclear if this was due to contraceptive failure or to errors in reporting of contraceptive use (Linac, et al., 2011).

Study Quality, Fertility Problems Outcome Measure and Bias

Table 3.3.5 shows the results of quality assessment (see table footnote for criteria). HIV was representative of the population and adequately assessed in all included studies, see Table 3.3.4. The non-HIV group (controls) were well defined, selected from the same population and exclusions were adequately reported in all included studies. Comparability of at least one confounder in the HIV/non-HIV groups was reported in all of the studies, and the majority of studies (6 of 7) reported on 'age'. The majority of the studies adequately evaluated and included confounders in the analysis (5 of 7). 'Fertility problems' outcome was adequately measured in all of the included studies, as indicated by blind or independent assessment. Overall the majority of studies had high quality as per quality assessment. Heterogeneity was significant in only one analysis, however, publication bias was not explored using funnel plots, Eggers test or trim and fill procedures because that analysis included two studies only, thus computation was not possible.

Percentages reported in Table 3.3.6 indicated that pregnancy occurred similarly in the HIV+ and HIV- women. However, more HIV+ women had amenorrhea, levels of FSH > 25 IU/l, infertility (>12months) and miscarriage than HIV- women.

Table 3.3.5.

Quality Ratings for the Ten Included Studies on the Basis of an Adapted Newcastle-Ottawa Quality Assessment Scale

Study	Quality Criterion						Overall rating ^g
	Adequacy of HIV (exposed) measure ^a Max 2 points	Adequacy of control (non-exposed), definition and selection ^b Max 2 points	Comparability of control ^c Max 2 points	Confounders adequately assessed Max 2 points ^d	Adequacy of outcome Fertility Problems measure ^e Max 1 point	None response rate or loss to follow-up ^f Max 1 point	
Cejtin, 2006	2	2	1	2	1	0	High
Chirgwin, 1996	2	2	1	1	1	NA	High
Gray, 1998	2	2	1	2	1	NA	High
Linan, 2011	2	2	1	2	0	NR	High
Willems, 2013	2	2	1	2	1	NA	High
De Muylder, 1990	2	2	0	1	1	NA	Average
Dhont, 2010	2	2	1	2	1	NA	High
Ross 2003	2	1	1	2	0	NR	Average
Yaro 2001	2	2	1	1	0	NA	Average
Ezechi 2010	2	2	1	1	1	NA	High

Note. NA = not applicable; NR = not reported; ^a HIV was adequately assessed when independent validation of the diagnosis (e.g. blood testing and/or hospital/medical records) and it was representative of the cohort i.e. drawn from the same population (up to 2 points); ^b Controls were adequately assessed when selection was comparable to cases, and HIV was excluded properly in the control population (up to 2 points); ^c Comparability of controls was achieved if exposed/non-exposed were matched or adjustment during analysis conducted. One point for *age* and one point for any other confounder (up to 2 points); ^d Confounders were adequately assessed if they were obtained from records or a blind interview, and one point was given if the same method was used for both groups (up to 2 points); ^e Fertility problems outcome was adequately assessed if independent or blind assessment was stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.) (up to 1 point); ^f Point given if same rate for both groups and <20% loss to follow up reported; ^g The overall quality rating was low (0 to 3 points), average (4 to 6 points), or high (7 to 10 points).

Table 3.3.6.

Number and Percentage of Women with a Specific Outcome in the HIV+ and HIV- Groups in the Included Studies (k=9)

Outcome	Number of women (%)	
	HIV+	HIV-
Pregnancy	532 of 1894 (28.1)	1120 of 4015 (27.9)
Amenorrhoea	173 of 3942 (4.4)	22 of 1292 (1.7)
FSH >25 IU/l	60 of 1194 (5.0)	10 of 317 (3.2)
Infertile > 12 months	107 of 146 (73.3)	432 of 780 (55.4)
Miscarriage	26 of 155 (16.8)	99 of 948 (10.4)

Note. FSH = follicle-stimulating hormone

Results of Meta-analyses

The first analysis compared two studies reporting ‘pregnancy’, see Figure 3.3.4. This meta-analysis showed a significant pooled effect size (OR 0.36, 95% CI 0.15 to 0.89) and significant heterogeneity ($I^2 = 97%$, $p < 0.00001$). The results indicated that the HIV+ women had significantly less pregnancies (more likely to have fertility problems) than HIV- women. Heterogeneity could not be explored with sensitivity or subgroup analysis because there were only two studies in this analysis.

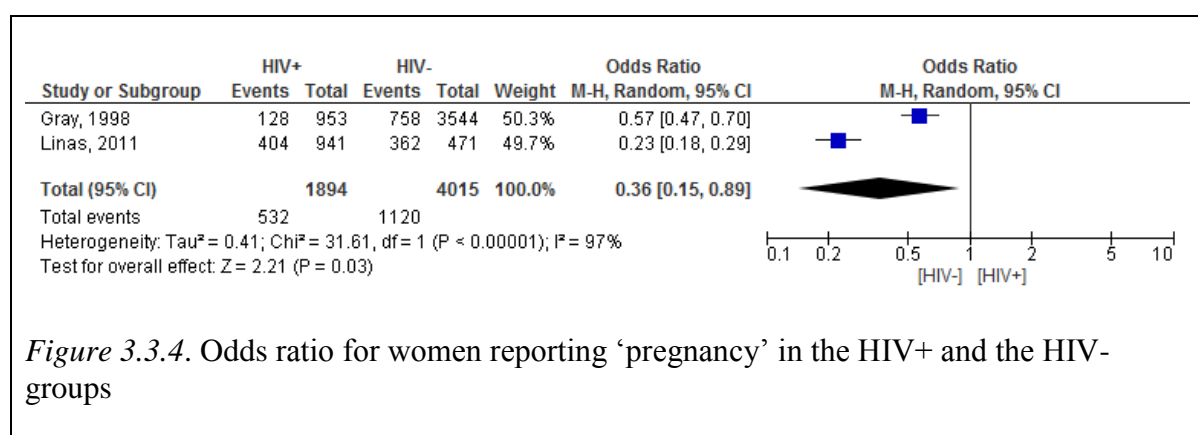
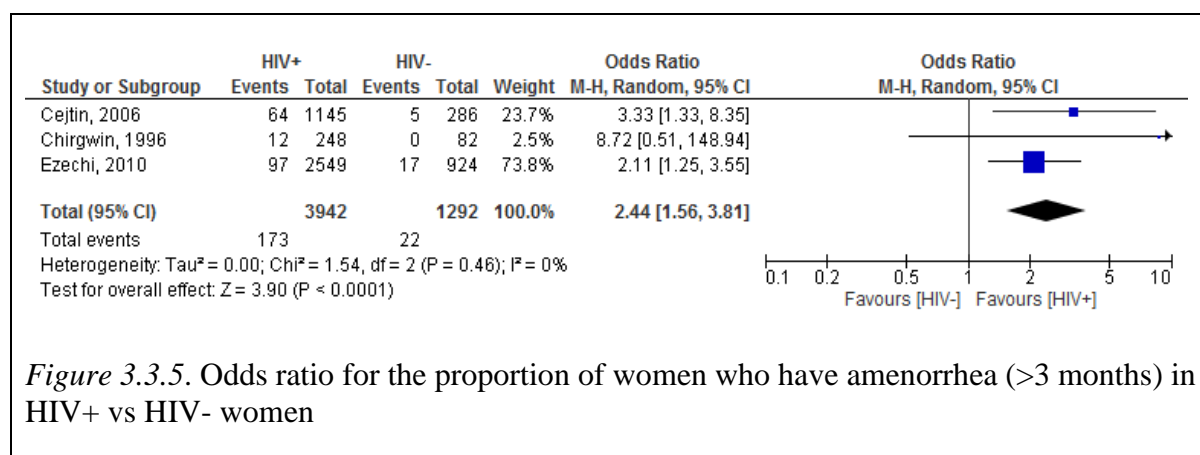
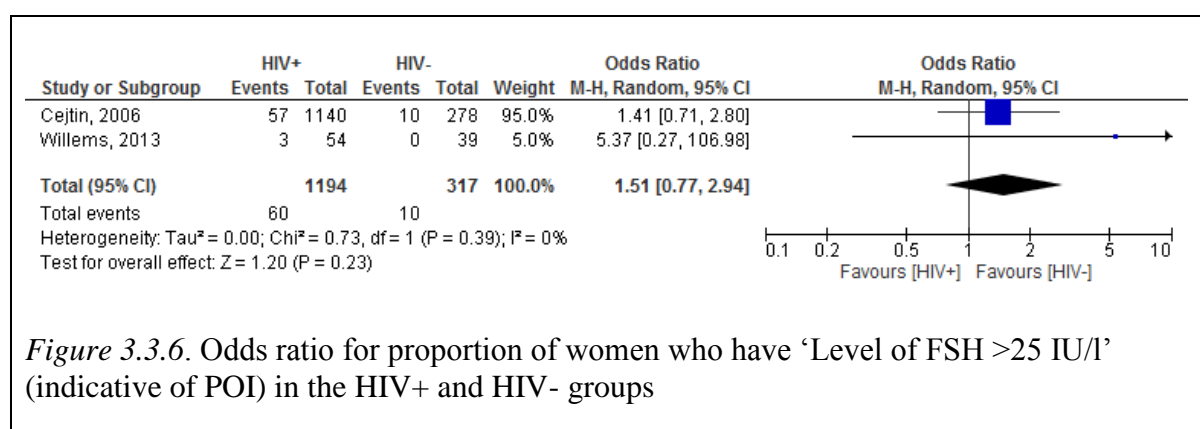


Figure 3.3.5 shows the forest plot and meta-analysis result for the three studies investigating the number of women who have had amenorrhea for more than 3 months. The meta-analysis showed a significant pooled effect size (OR 2.44, 95% CI 1.56 to 3.81), and

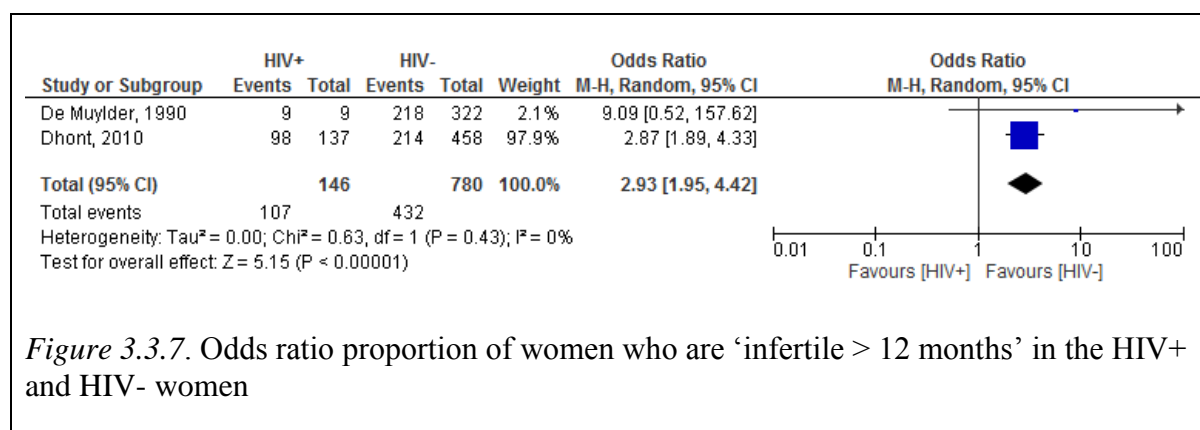
non-significant heterogeneity ($I^2 = 0\%$, $p = 0.46$), see Figure 3.3.4. The results indicated that the HIV+ women had significantly more amenorrhea (more likely to have fertility problems) than the non-HIV group.



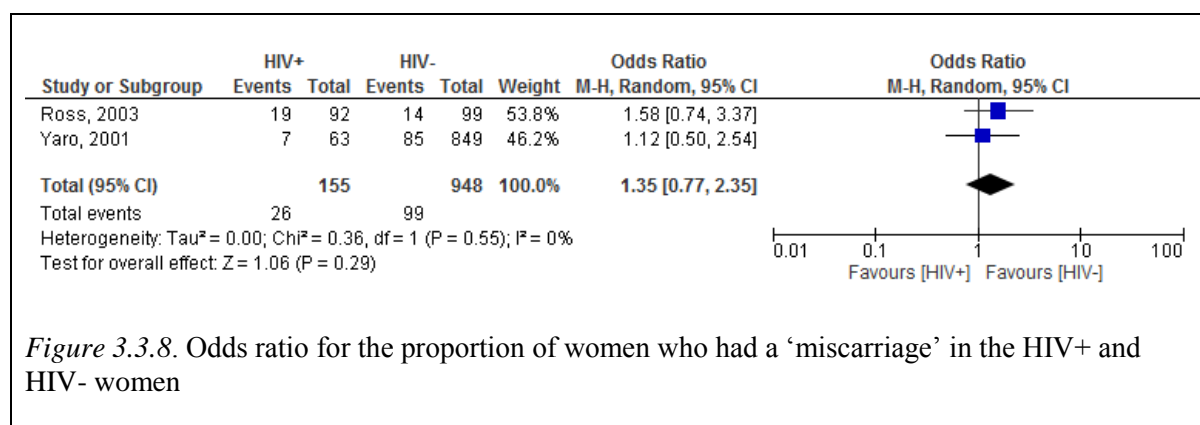
The third analysis compared two studies reporting ‘FSH >25 IU/l’, see Figure 3.3.6. The meta-analysis showed a non-significant pooled effect size (OR 1.51, 95% CI 0.77 to 2.94), and non-significant heterogeneity ($I^2 = 0\%$, $p = 0.39$). The results indicated that the proportion of women who had ‘FSH > 25 IU/l’ did not differ significantly between the HIV+ and HIV- groups (comparable fertility problems).



The fourth analysis compared two studies with calculated data representing the proportion of infertile (>12 months) women in the HIV+ and HIV- women, see Figure 3.3.7. The meta-analysis revealed a significant pooled effect size (OR 2.93, 95% CI 1.95 to 4.42), with non-significant heterogeneity between studies ($I^2 = 0\%$, $p = 0.43$). The results indicated that there were more infertile women in the HIV+ group than the HIV- group (more likely to have fertility problems).



The fifth analysis compared two studies reporting on the proportion of women who had a ‘miscarriage’ in the HIV+ and HIV- groups, see Figure 3.3.8. The meta-analysis revealed a non-significant pooled effect size (OR 1.35, 95% CI 0.77 to 2.35), with non-significant heterogeneity between studies ($I^2 = 0\%$, $p = 0.55$). The results indicated that the two groups were equally likely to report miscarriages (comparable fertility problems).



Publication bias assessment.

Heterogeneity was only significant in one of the four analyses, however publication bias could not be assessed using funnel plots, Eggers test or trim and fill procedures because this analysis included only two studies, which precluded all computations.

Discussion**Principal Findings**

The results of the present set of meta-analyses suggest that HIV may be a relevant factor for the prediction of ability to become pregnant, due to the lower pregnancy rate and higher rate of infertility and amenorrhea. These results support an impact via the first four pathways (inability to achieve pregnancy) but not the fifth pathway (miscarriage) in Figure 3.3.2 (pp. 152). Results support the first (anovulation) and third (contraception) pathways but not the second pathway (TFI). However, the second pathways was not examined due to a lack of primary studies reporting on STIs and TFI in HIV retrieved from current search. The first pathway appears more likely to be due to weight loss than POI because the results for the FSH analysis were not significant. The third pathway also requires more research to confirm the exact use of contraception and abstinence and possible association with pregnancy.

Potential reasons for the decreased rate of pregnancy reported in HIV+ women, include hormonal problems (menstrual irregularities, POI), decreased sexual activity, increased use of contraceptives, and mechanisms pertaining to the disease, its symptoms and comorbidities like STIs (Waters, et al., 2007; van Leeuwen et. al., 2007; Kushnir & Lewis, 2011). Significant results of ‘pregnancy-rate’ analysis need to be interpreted in light of the fact that a proportion of the sample were contracepting and that amenorrhea analysis was significant while FSH level was not. The difference in pregnancy rate across the two included studies should also be taken under consideration. In one study (Gray et al., 1998) the

pregnancy rate in both groups (HIV+ 13.4%, HIV- 21.4%) was lower than the other study (HIV+ 25.7%, HIV- 45%) [Linas et al., 2011]. This difference may have been due to methodological differences in the two studies, where data was collected at one point in time in the Gray et al. (1998) study and over time (7 years) in the Linas et al. (2011) study. Cross-sectional studies may therefore underestimate the ability to eventually achieve pregnancy in both groups (HIV+ and HIV-), because they only capture current fertility problems rather than lifetime. Nevertheless, women with HIV were less likely to be pregnant overall.

Overall it can be inferred from the results that what difference there is in infertility and pregnancy rate could be related to lack of period and/or contracepting. It seems plausible that the amenorrhea may be associated with low weight specifically and/or ill health in general (Lo & Schambelan 2001; Kushnir & Lewis, 2011). Amenorrhea does not appear to be related to direct effect of HIV or other ‘opportunistic infections’ on ovarian function/hormones such as FSH, contradicting suggestions in the literature of ovarian impairment (van Leeuwen et. al., 2007; Kushnir & Lewis, 2011). Rather the results corroborate explanations in the literature indicating that amenorrhea may be an indirect effect of the subsequent wasting/weight loss, comorbid drug use, marijuana, chronic alcohol consumption, low SES (Lo & Schambelan 2001) or low CD4 count and high HIV viral load (Waters, et al., 2007). The significant link between HIV and amenorrhea is not surprising given that weight loss starts at early stages of HIV and is not only limited to end stage or AIDS manifestation, see Table 3.3.1. The effect of stage of disease and related sequel could not be confirmed because analysis by stage was not feasible due to lack of relevant data.

An understanding of how contraceptive use may have influenced the lower rate of pregnancy would have been gained from subgroup analysis based on only non-contracepting women. Although subgroup analysis was planned it was not possible because in one of the included studies the number of pregnancies exceeded the number of non-contracepting

women, indicating that some women became pregnant while using contraceptives, suggestive of misuse/failure of contraceptives or an over reporting of contraceptive use.

In the present study the effect of HIV on fertility was examined in a set of meta-analyses of observational studies. This systematic approach demonstrated that HIV was associated with infertility and reduced pregnancy rate but a causal relationship could not be confirmed, nor could a specific mechanism of action be specified. Additionally, application of the 'Bradford Hill criteria' noted in the General Methods (pp. 55), lead to the conclusion that the available evidence does not meet any of the criteria, therefore the likelihood of a causal relationship between HIV and fertility problems could not be confirmed. It is possible that this is because there are numerous confounding factors such as comorbidities and lifestyle factors such as abstinence that need to be well controlled for to enable firm conclusions about causality.

Justification for including HIV in the FertiSTAT.

Although the results showed that HIV did not appear to be related to FSH levels suggestive of POI (FSH > 25) as can be inferred from the lack of significance of the analysis of FSH level, results cannot be used to confirm whether the impact was via amenorrhea exclusively. The similar levels of FSH in HIV+ and HIV- women further corroborates that the amenorrhea may be induced by side-effects of the disease such as weight loss or comorbidities such as drug use (Waters, et al., 2007; Kushnir & Lewis, 2011), thereby weakening the argument that ovarian dysfunction is the causal pathway involved. If the mechanism of action of HIV was only via amenorrhea, then it would not be an independent risk factor since amenorrhea is a risk factor in the current FertiSTAT and the inclusion of HIV would therefore not increase the predictive ability of the tool. If the mechanism of action had been via hormonal change indicative of ovarian dysfunction (POI), then HIV may have had an independent effect on fertility problems. Confirmation of the other two causal

pathways (tubal damage, contraception) thorough which HIV may exert an impact on fertility problems could not be ascertained from the available data as there were no studies examining tubal damage, rate of intercourse and abstinence found in the current search. The fact that the meta-analysis for ‘miscarriage’ showed no significant difference between HIV+ and HIV- women indicated that HIV may have little impact once pregnancy occurs. Finally, the increased likelihood of being infertile in the HIV+ women indicated that HIV may be one of the factors contributing to the infertility, and the mechanism via which it contributes appeared to be via lack of period, abstinence or contraceptive use. Additionally, this association may be linked to increased susceptibility to, or comorbidities with STIs and PID (Waters, et al., 2007; van Leeuwen et. al., 2007; Kushnir & Lewis, 2011), unfortunately there was no data to corroborate this information.

The current meta-analyses indicated that inclusion of HIV in FertiSTAT as a new risk factor could potentially increase prediction of fertility problems in LMICs. In the present study the effect of HIV on fertility was examined according to the fertility dimension of outcome i.e. infertility, pregnancy rate, amenorrhea and FSH level. This systematic approach demonstrated that although HIV had an impact on infertility and pregnancy rate this impact could be affected both by lack of period and use of contraceptives. Given the significant result of the meta-analysis using ‘infertility’, ‘pregnancy rate’ and ‘amenorrhea’ but not of FSH level, it can be inferred that HIV has an impact on menstrual cycle but that it does not appear to be associated with ovarian function. The effect on pregnancy rate has to be interpreted in light of the fact that a proportion of couples in those studies were contracepting making it difficult to disentangle the effect of HIV on ability to become pregnant.

Implications of Findings

Results of the current study indicated that awareness of the risks associated HIV should be communicated to women. The implications of these results is that women and health care providers should be made aware of potential risks to reproductive health that women who have HIV face. The results of the review lend support to reports in the literature of increased likelihood of menstrual irregularities that can hinder a women's ability to become pregnant (Lo & Schambelan 2001; Waters, et al., 2007; van Leeuwen et. al., 2007; Kushnir & Lewis, 2011). The repercussions of the accompanying amenorrhea for couples wanting to become pregnant are important because of its impact on childbearing. An understanding of whether the amenorrhea is related to the disease or side-effects/ comorbidities such as weight loss and drug use needs to be examined as the treatment will vary depending on what the amenorrhea is attributable to. The distinction between amenorrhea linked to decreased ovarian function and that which is related to weight/drug use, is that the former may not be reversible while the latter can potentially be remedied. Thus from a clinical perspective it is important to measure levels of FSH in HIV+ women who have amenorrhea and desire to have children to rule-out POI and advise the patient accordingly.

HIV in pre-pregnancy care.

The importance of including HIV in pre-pregnancy care was underlined in the WHO report "Meeting to Develop a Global Consensus on Preconception Care to Reduce Maternal and Childhood Mortality and Morbidity" (WHO, Meeting report, 2012). Additionally, emphasis was placed on tailoring interventions to settings (before attempting implementation) depending on local prevalence, the existing interventions, and the available mechanisms and resources that can facilitate the delivery of additional care. With regard to

HIV specifically, the report included information on the association between HIV and infertility and effects of unprotected sexual intercourse on ability to get pregnant in populations at high risk of HIV/STIs. It was noted that due to limited access to infertility treatment people with fertility problems often resort to traditional methods of self-cure (e.g. unprotected sex with multiple partners to achieve pregnancy), which can result in the spread of HIV. It was also noted that in developing countries couples living with HIV have higher rates of infertility and spontaneous miscarriage (no data reported). One of the health problems contributing to maternal and child morbidity and mortality mentioned in the report was the lack of HIV/STI screening and the repercussion on future fertility (via PID, tubal damage, see Figure 3.3.2). People living with HIV were mentioned in the report as a special segment of the population that should be targeted with pre-pregnancy care. However, specific recommendation, symptoms and effects of HIV that could potentially be mediating the impact on fertility problems were not mentioned. The results of the current meta-analysis indicated that HIV+ women were more likely to have amenorrhea (a potential consequence of HIV that impedes pregnancy), demonstrating the importance of including amenorrhea as an additional aspect of a comprehensive pre-pregnancy package.

The inclusion of HIV in a comprehensive pre-pregnancy care package was further emphasized in the WHO's publication: "Preconception care: maximizing the gains for maternal and child health" (WHO, Preconception care, 2013). It was reported that this can help prevent the vertical transmission of HIV/STIs. Interventions for HIV in the pre-pregnancy care package include essential aspects such as the prevention of mother-to-child transmission of HIV, family planning and contraception but do not include how to safely become pregnant while HIV positive (especially important for serodiscordant couples to prevent the transmission of HIV).

Strength and Limitations in Included Studies

The heterogeneity in study methodology, outcome measures and sample size in included studies could affect the comparability of these studies, and the generalizability of the results of this review. Heterogeneity in fertility problems outcome (inability to become pregnant, lack of period, hormonal changes), study design (case-control, cohort and cross-sectional) and data collection methods (medical examinations and interviews), can affect the practical applicability of the results. However, heterogeneity was only statistically significant in one meta-analysis in this review, indicating that overall issues of methodological heterogeneity may not be extensive. The quality of each study independently does not appear to affect the overall results of the review since all of studies were of sound quality.

Bias relating to the primary studies included selection bias, information bias and recall bias. In the hospital based studies, the selection of participants based on hospital attendance can reduce the generalizability of the results. However, because the same sampling procedures were used for both cases (exposed) and controls (non-exposed), we can assume that selection bias may not be substantial. It can be assumed that since the selection of participants was from the same sample and information was gathered using the same method for both the exposed and non-exposed groups in all the studies, that selection and information bias may not affect results considerably. Recall bias can affect the internal validity of results where data was collected in interviews that require recall of old events, which is more substantial for recall of details (Hassan, 2005). Thus, recall bias might not have been considerable because the interviews did not require recall of old events e.g. information on last menstrual cycle. Bias due to confounder was a potential limitation of the studies included but it might not have been considerable given that matching the groups for confounders was reported in all of the included studies and including confounders in the

analysis, was conducted in five of the seven studies. The most important confounder 'age' which is known to impact negatively on fertility was included in the analysis of five studies. There could have been an unequal distribution of other confounders in the exposed and non-exposed groups but this was not reported in the included studies. However, the effect of confounders like weight, stage of HIV, education and SES that could have influenced the relationship between HIV and fertility problems was taken into consideration via either matching groups for confounders or entering them into analysis. Another limitation relating to the primary studies is the use of observational designs, as discussed in previous reviews. As in the case of consanguinity randomization would not have been possible or ethical, for HIV, therefore the most rigorous design would be cohort studies, followed by case-control and then cross-sectional (Mann, 2003). This study comprised of three cohort studies, two case-control studies and cross-sectional data in two studies, which are reasonably rigorous in identifying associations (Mann, 2003), thus the results of this review can only be used to infer association.

Future Research

Future research to disentangle the effect of HIV on fertility problems requires prospective cohort and case-control studies to investigate the causal mechanisms that are involved. Future research can be informed by the pathway diagram, Figure 3.3.2 (pp. 152), indicating that studies should examine the use of contraception and abstinence as well as STIs and TFI in HIV. Studies need to consider the different stages of HIV and ensuing side-effects such as wasting and to determine which aspects of the reproductive process are affected. Future research should be directed at understanding the reasons for the increased infertility and lower pregnancy rate, to definitively ascertain if it is related to abstinence, sexual frequency, use of condoms or menstrual irregularities and amenorrhea.

Finally, it's important to investigate the link between HIV and POI due to the small number of included studies in the current meta-analysis. It is imperative that after more such studies are carried out that an update of the meta-analyses be conducted. Ideally, longitudinal prospective cohort studies should be conducted to follow women who are HIV+ and HIV- controls, with measurements at baseline and follow-up of fertility problems outcomes such as pregnancy, childlessness, menstrual irregularities, and POI. The intent to conceive, use of contraceptives, frequency of sexual intercourse as well as the duration of exposure to sexual intercourse should be reported. Additionally, confounders such as age, stage of the disease (clinical staging and CD4 count), weight, comorbid STIs and drug use and SES should be considered (matching and/or included in the analysis).

Conclusion

Fertility problems have been reported as a negative consequence of HIV in the literature but evidence to support this claim has been limited. Results of the current meta-analyses indicated that HIV may affect ability to become pregnant. Therefore, the results indicated that including HIV may increase the predictive ability of the FertiSTAT. It is important to note that this area of research should be re-examined due to the methodological limitations of primary studies and the small number of included studies in the meta-analyses.

Study 3.4: Systematic Review and Meta-analysis of Observational Studies Examining the Association of Genital Tuberculosis and Fertility Problems

Introduction

Genital tuberculosis was one of the risk factors endorsed by survey of fertility doctors (Chapter 2, pp. 25). The validity of this risk factor as a predictor of fertility problems was examined in the current systematic review using the operational definitions of fertility problems and risk factor applied in the original development of FertiSTAT (Bunting & Boivin, 2010).

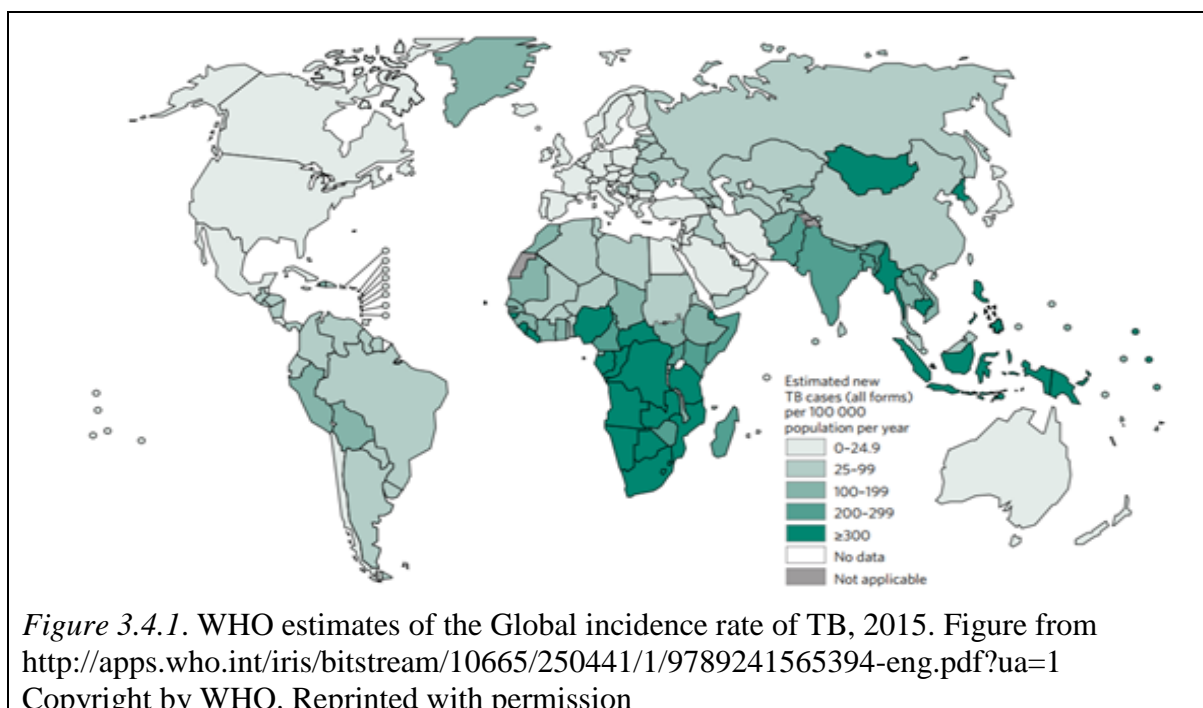
Description of GTB

Tuberculosis (TB) is an infectious airborne disease caused by the bacillus mycobacterium tuberculosis (WHO, Global TB report, 2015). TB is mainly prevalent in developing countries, with 75% of all cases occurring in only 13 developing nations (Haas, 2000). According to WHO estimates, in 2014, 3.2 million women contracted TB (WHO, TB in women: factsheet, 2015). India has the highest incidence of TB in the world and Nigeria the highest in Africa, with very low incidence in developed countries (WHO, Global TB report, 2015). According to the WHO (TB in women: factsheet, 2015), TB mostly affects vulnerable groups; those living in poverty, malnutrition and food insecurity, and the vast majority of TB deaths occur in the developing world.

TB can manifest as pulmonary TB in the lungs and extrapulmonary TB occurring outside the lungs (WHO, Global TB report, 2015). In very rare cases maternal TB can pass to the foetus if there is rupture of part of the placenta or the infected endometrium, and this type is referred to as congenital TB (Hüseysin, Melike, Sevgi, Onur & Rahmi, 2009).

Extrapulmonary TB occurs as a result of the spread of TB from the lungs to other organs

through the blood, which can transpire within hours of the initial infection (Varma, 2008). Genital tuberculosis (GTB) is one manifestation of extrapulmonary TB that happens as a result of the spread of TB to the genital tract through the blood or from neighbouring lesions (Gatongi et al., 2005; Varma, 2008). GTB represents between 15-20% of extrapulmonary TB and affects about 12% of people who have pulmonary TB (Aka & Vural, 1997). Estimates of the prevalence of GTB cannot be precisely ascertained because the disease can be asymptomatic and remain undetected for years (Gatongi et al., 2005; Chowdhury, 1996, Varma, 2008; Ghosh, Ghosh & Chowdhury, 2011), see Figure 3.4.1 for global incidence rate of TB. According to the WHO, GTB is a challenge to diagnose and has been recognised as an important cause of infertility in settings with high TB-incidence (WHO, TB in women: factsheet, 2015). The global prevalence of GTB in infertile women has been estimated to be between 5-10% (Figueroa, Martinez, Villagrana & Arredondo, 1996), as low as 1% in Australia and as high as 19% in India (Chowdhury, 1996).



GTB can affect any of the organs of the female reproductive tract, but the fallopian tubes are the most susceptible site, from which it spreads to other parts (Varma, 2008). It is reported in the literature that the involvement of the fallopian tubes in nearly 100% of cases suggests that they may be the initial source of infection (Varma, 2008). GTB has been noted most commonly in the fallopian tubes (95–100%), endometrium (50–60%) and ovaries (20–30%), with much less involvement of the cervix (5–15%), vulva/vagina (1%) and the myometrium [2.5%] (Schaefer, 1976; Varma, 2008; Ghosh et al., 2011). In some reports cervical involvement was reported to be higher, 43.1% (Samal, Gupta & Agarwal, 2000) and 24% (Nogales-Ortiz, Tarancion & Nogales, 1979), endometrial involvement was higher, 79% (Nogales-Ortiz et al., 1979) and 60% (Onuigbo, 1979), while ovarian involvement was lower, 11% (Nogales-Ortiz et al., 1979).

The diagnosis of GTB can be performed via several tests including histology, culture, polymerase chain reaction (PCR), laparoscopy, hysteroscopy and hysterosalpingography depending on availability in the clinical setting. Histology refers to microscopic examination of tissues, while culture refers to growing a microbe in the lab to help identify it, both of which are not as specific as PCR, a test that analyses the DNA of the microorganism to identify it (Srivastava et al, 2014; Thangappah, Paramasivan & Narayanan, 2011).

Laparoscopy is a surgical procedure that involves inserting a narrow tube with a light and camera through a small abdominal incision, while hysteroscopy involves using a similar instrument inserted through the vagina into the uterus (NHS Choices, Hysteroscopy, 2016). Hysterosalpingography is an examination of the female reproductive tract using a specific type of x-ray that requires the use of contrast material (Baramki, 2005). The Centres for Disease Control (CDC) and National Institute for Health and Care Excellence (NICE) guidelines recommend that diagnosis should be confirmed by culture after initial microscopic identification of the microorganism (CDC, Diagnosis of TB, 2016; NICE, Guidelines

[NG33], 2016). In addition to culture, PCR has been used more recently to confirm the diagnosis as it is more specific (Varma, 2008) but it is yet to be included in guidelines. Not only is PCR more precise (high sensitivity and specificity) it is also faster (days or even hours) than culture [several weeks] (Gatongi et al., 2005; Varma, 2008; Ghosh et al., 2011). These confirmatory tests (culture, PCR) are usually limited in low resource countries where the prevalence of GTB is highest (Giannacopoulos et al., 1998; Lamba, Bryne, Goldin & Jenkins, 2002; Qureshi, Sammad, Hamd & Lakha, 2001), therefore, the diagnosis is done during hysteroscopy, laparoscopy or hysterosalpingography usually performed during preliminary infertility investigations (Gaur, Meheshwari & Lal, 1983; Samal et al., 2000; Margolis, Wranz, Kruger, Joubert, & Odendaal, 1992). Clinical examination of the reproductive tract shows that GTB manifests as a mass or lesion [adhesions, nodules, tubercles] (Ahmadi, Zafarani & Shahrzad, 2014; Gatongi et al., 2005; Varma, 2008; Ghosh et al., 2011). Laparoscopy and hysteroscopy provide visual assessment of such lesions and can be useful for obtaining tissue biopsy for culture and histology (Gogate, Joshi & Gogate, 1994; Thangappah et al., 2011). Tissue can also be obtained from menstrual fluid in the first day of menstruation to confirm diagnosis (Oosthuizen, Wessel & Hefer, 1990; Kirchoff, 1951). One of the major problems with diagnosing GTB is that it can remain asymptomatic (dormant state, or no observable symptoms) for one to ten years (Simon, Weinstein, Pasternak, Swartz & Kunz 1977; Daly & Monif, 1982; Burne, 1956) and is typically only discovered and diagnosed during routine infertility investigations (Figuroa et al., 1996; Gatongi et al., 2005; Varma, 2008). Therefore, a history of general ill health, weight loss, low-grade fever, fatigue or vague lower abdominal discomfort is the typical profile to alert healthcare providers to the presence of GTB (Varma, 2008).

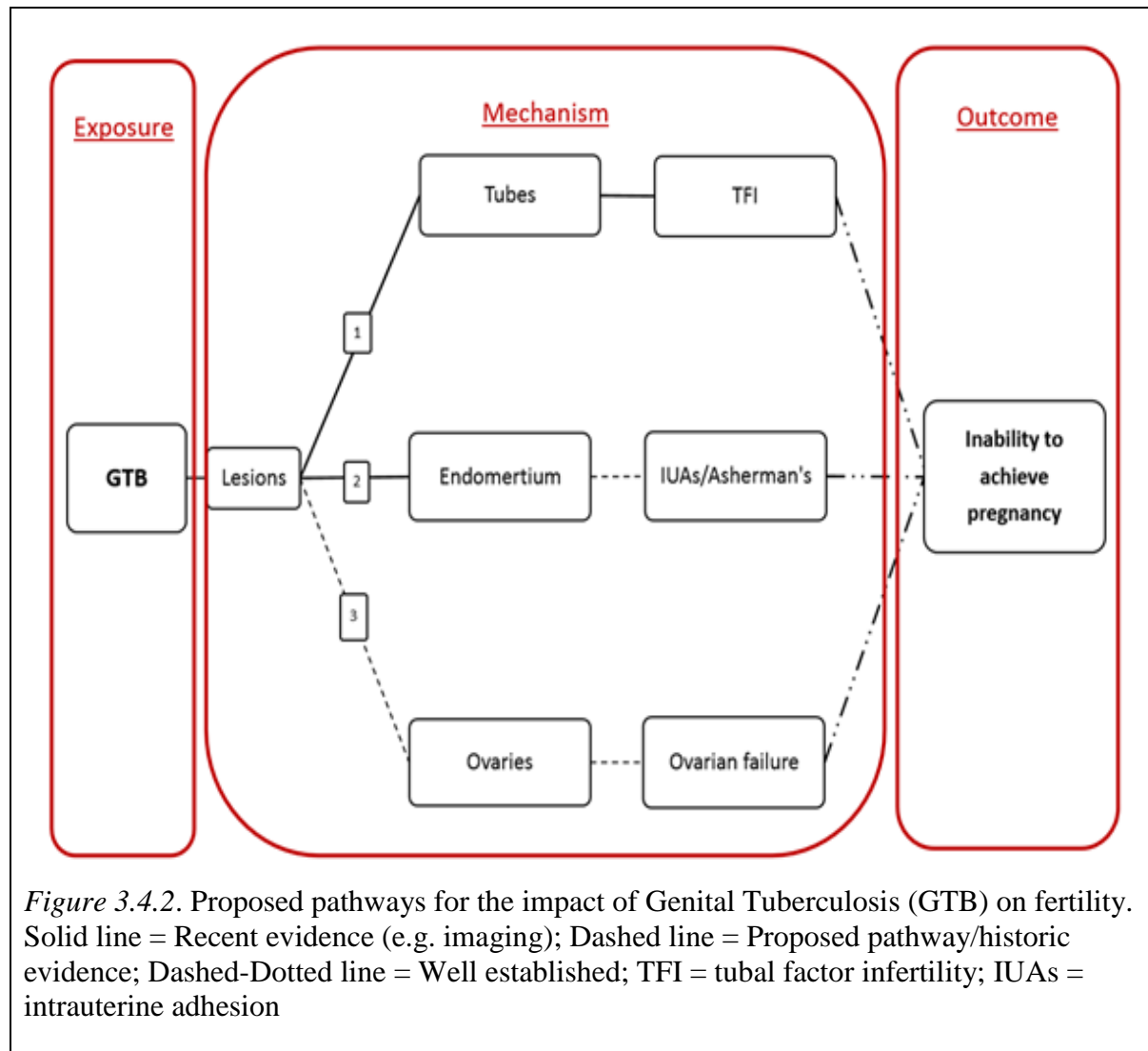
It has been reported that 20% of GTB patients have a family history of TB in their immediate family members, suggesting exposure during childhood (Schaefer, 1976) and that

approximately 50% have had other forms of TB in their lifetime (Varma, 1991; Tripathy & Tripathy, 1987; Schaefer, 1976). The majority (80-90%) of cases diagnosed in developing countries have been shown to be between the age of 20 and 40 years old (Schaefer, 1976; Falk, Ludviksson & Agren, 1980; Hutchins, 1977; Tripathy & Tripathy, 1987; Ojo & Unuigbe, 1987; Nogales-Ortiz et al., 1979). In developed countries reports have shown an older age, over 40 years (Falk et al., 1980; Hutchins, 1977). A delay in menarche in women with GTB (13.7 years old) has also been reported in a study where a group of women with GTB were compared with women with PID and endometriosis (12.8 years old) combined (Avan, Fatmi & Rashid, 2001). It has also been reported in a historical study using hospital records, that when pulmonary TB occurs close in time to menarche, this increases the likelihood of genital tract involvement (Burne, 1956).

Plausible Mechanisms to Explain why GTB Could be Associated with Fertility Problems

In addition to an association between GTB and infertility, reports in the literature of laparoscopic and hysteroscopic findings confirm that GTB is associated with the formation of lesions in the tubes, endometrium and ovaries, leading to tubal blockage, endometrial destruction and ovarian masses (Ahmadi et al., 2014; Chavhan, et al., 2004; Ghosh et al., 2011; Varma, 2008; Tripathy & Tripathy, 1998), see Figure 3.4.2. Since GTB can remain asymptomatic long after the initial infection and only exhibits symptoms once it has damaged the reproductive organs extensively (Figueroa et al., 1996; Gatongi, et al., 2005; Varma, 2008; Ghont, et al., 2011), it is hard to extrapolate the exact biological pathway involved. However, it appears that there are three plausible mechanisms of change, see pathways 1, 2 and 3 in Figure 3.4.2. The first through tubal blockage (Ahmadi et al., 2014; Chavhan, et al., 2004) is the most probable pathway since fallopian tubes are the site of the majority of GTB (Schaefer, 1976) and the extent of damage to the tubes has been demonstrated in imaging

described in the literature (Ahmadi et al., 2014; Chavhan, et al., 2004; Malik, 2003; Tripathy & Tripathy, 1998).



The second mechanism involving the endometrium, may have no impact if the damage is not extensive since the endometrial cells are shed with menstrual blood monthly (Nogales-Ortiz et al., 1979). Extensive endometrial damage on the other hand, can lead to menstrual disturbances and amenorrhea, due to the development of intrauterine adhesions (IUAs) and ultimately Asherman's syndrome (Sharma, et al., 2008). Asherman's syndrome is characterised by adhesions that occur in the uterine cavity or the cervix. Typically

Asherman's occurs as a result of damage to the endometrium from curettage or infection but it has also been shown to be associated with GTB (Yu, Wong, Cheong, Xia, & Li, 2008).

The syndrome can be diagnosed by ascertaining the presence of IUAs during hysteroscopy (Yu, et al., 2008). Clinical features of Asherman's syndrome include menstrual disturbance (scanty or painful periods), amenorrhea, fertility problems, recurrent miscarriage and placental problems (Yu, et al., 2008).

In the third mechanism, ovarian damage caused by lesions in the interior of the ovaries or encapsulation from the outside may result in the disruption of ovulation (ovarian failure), which would preclude pregnancy. The occurrence of amenorrhea in GTB can be due to ovarian failure, however complete destruction of the ovaries is rarely found (Varma, 2008). Therefore, amenorrhea in GTB has usually been attributed to extensive damage to the endometrium rather than ovarian damage (Malkani, 1966; Nogales-Ortiz & Villar, 1957). Infertility in GTB can occur with or without amenorrhea and regardless of the cause of the amenorrhea. In cases without amenorrhea, the infertility is usually attributed to tubal damage (Varma, 2008).

Reproductive Health Consequences of GTB

It appears from the literature reviewed that the association between GTB and infertility is a well-established fact, however, an in depth evaluation of this literature would suggest that the evidence is not unequivocal. There are numerous studies and reviews reporting on the association of GTB with infertility, menstrual irregularities and other reproductive outcomes. A summary of the consequences reported in four narrative reviews (Malik, 2003; Gatongi et al., 2005; Varma, 2008; Ghosh et al., 2011) based on 29 primary studies, is presented in Table 3.4.1. The reviews summarized were subjected to quality evaluation using the "Critical Appraisal of Systematic Reviews" published by the WHO

(Abalos, Carroli, Mackey & Bergel, 2001). Table 3.4.1 presents information on the reproductive outcomes (infertility, pelvic pain, menstrual dysfunction, Asherman's and TB in the neonate), how TB impacts the reproductive outcome and the percentages (prevalence of the problem) reported. Reference for the primary studies cited and the reference for the review are also shown in the table. Generalizations about the health consequences noted in Table 3.4.1 need to be considered in light of the methodology of the reviews and the primary studies included. The most important methodological drawback of the reviews was the absence of a description of the search methodology (Malik, 2003; Gatongi et al., 2005; Varma, 2008). In the Ghosh et al. (2011) review, PubMed, Medline and Indian Indexing Software Medline were searched. However, search methodology was not reported in the other reviews. The most important flaw in the primary studies reviewed was the lack of control groups or the study of GTB in infertile women exclusively, making it difficult to infer causality or to determine statistical comparisons such as odds ratio.

Table 3.4.1.

Summary of Reproductive Health Consequences of Genital Tuberculosis (GTB) Reported in the Literature

Reproductive Outcome	Effect of GTB	Statistics reported (percentage of GTB patients)	Primary study	Review
Infertility	Infertility is the presenting or most common complaint	40 to 50	Siegler, 1979; Sutherland, 1979; 1983, Bazax-Malik, 1983; Sivanesaratnam, 1986; Punnonen, 1983; Francis 1964; Govan, 1962; Russel, 1951	Varma, 2008
	Infertility	64.2 vs. 22 control	Tripathy & Tripathy, 1987	
		54.4	Ojo & Unuigbe, 1987	
		10 to 85	Schaefer 1976, Krishna, 1977; Tripathy & Tripathy, 2002	Ghosh, 2011
		NR	Arora, 2003; Choudhary, 1996; Bukulmez, 1999; Bapna, 2005; Varma, 1991; Sharma, 2008; Chavan, 2004; Dam, 2006	Ghosh, 2011
		NR	Dhillon, 1990; de Vynck, 1990	Varma, 2008
	Infertility (primary and secondary)	42.5 (78 and 22)	Qureshi et al., 2001	Gatongi, 2005
Tubal blockage (Peritubal adhesions and tuboovarian masses)	47.2	deVynck et al, 1990	Malik, 2003	
Pelvic pain	Is not usually severe and present for many months before presenting	25 to 50	Falk et al., 1980; Francis, 1964; Sutherland, 1979; Sutherland, 1983	Varma, 2008
	Progression of GTB increase severity of pelvic pain and is usually aggravated by coitus, exercise, and menses.	NR	Daly & Monif, 1982	Varma, 2008
	Chronic pelvic pain	42.5	Qureshi et al., 2001	Gatongi, 2005
	Chronic pelvic pain	15.8	Samal et al., 2000	Gatongi, 2005
Menstrual dysfunction	Abnormal uterine bleeding	10 to 40	Simon et al., 1977; Daly & Monif, 1982	Varma, 2008
	menorrhagia (very heavy)	19	Samal et al., 2000	Varma, 2008, Ghosh, 2011; Gatongi, 2005
	Oligohypomenorrhea	54	Samal et al., 2000	Varma, 2008; Gatongi, 2005
	Amenorrhea	NR	Sharma, 2008	Ghosh, 2011

Reproductive Outcome	Effect of GTB	Statistics reported (percentage of GTB patients)	Primary study	Review
	Amenorrhea	14.3	Samal et al., 2000	Varma, 2008; Ghosh, 2011; Gatongi, 2005
		15	Qureshi et al., 2001	Gatongi, 2005
	Dyspareunia (painful sex)	5	Qureshi et al., 2001	
	Dysmenorrhoea (painful period)	12.5	Qureshi et al., 2001	
	Menstrual irregularities found cases of endometrial TB of which Amenorrhea was the most common	85 and 43.6	Tripathy & Tripathy, 1987	Varma, 2008; Gatongi, 2005
Asherman's Syndrome	Uterine adhesions can be the cause of infertility	NR	Sharma, 2008; Bukulmez, 1999	Ghosh, 2011
TB in the neonate	TB can be spread to fetus in utero/delivery from a mother who has GTB (referred to as congenital TB)	NR	Hamadeh,1992; Arora, 2003; Stark, 1997; Cantwell, 1994	

Note: NR=not reported

It can be inferred from the data reported in Table 3.4.1 that there is a range of problems that seem to be associated with GTB, however there is heterogeneity in the prevalence of these problems. Overall, the data strongly suggest that GTB was found to be associated with reproductive health consequences like infertility (approximately 50% of women with GTB), pelvic pain (approximately 30% of women with GTB) and menstrual disturbances (approximately 30% of women with GTB) in the primary studies. Inferences about the data in Table 3.4.1 need to be made cautiously due to methodological shortcomings such as lack of control groups and clear terminology, and inconsistent reporting of outcomes, which could affect the validity of the results. Although infertility is reported in approximately 50% of GTB cases the validity of this association cannot be ascertained as none of these studies (except one) had control groups, highlighting the need to systematically evaluate the evidence and to perform meta-analyses where data is present.

Rational, Aim and Objectives

It was evident from the literature that GTB has negative consequences on women's reproductive health, most notably infertility, menstrual dysfunction and pelvic pain (Malik, 2003; Gatongi et al., 2005; Varma, 2008, Ghosh et al., 2011). However, the lack of unequivocal evidence to support an association between GTB and infertility suggests the need to verify the presence of such an association, its magnitude, the biological mechanism involved and the link with severity of GTB.

The biological plausibility of the effect of GTB coupled with the results of the survey of physicians [GTB endorsed as a potential risk factor by 97% of responders] (Chapter 2, pp. 25) highlighted the need to investigate whether GTB should be included in the adapted FertiSTAT. The objective of the review was to examine whether GTB was associated with fertility problems in women, and at what point in the reproductive process GTB might exert

its impact. The population of interest for the review was women, the exposure was GTB and the outcome of interest was fertility problems. In the present review meta-analyses were performed according to the outcomes available in the literature to determine the effect of GTB on ability to become pregnant. The overall aim of this review was to determine whether GTB should be included as a new risk factor in the adapted FertiSTAT.

Materials and Methods

Search Strategy

The search terms included words related to GTB, for a complete list of MeSH terms see Appendix M. Studies were excluded if the TB was pulmonary or congenital only.

Data Extraction and Quality Assessment

The data extraction form (Appendix H) was adapted to include information relevant to GTB. The NOS form was adapted to reflect quality criteria for the assessment of GTB and additional confounders. GTB was adequately assessed if diagnosis was confirmed through culture or PCR. The confounder that was more important than others was rural vs. urban living (potentially affecting rate of infection and/or help-seeking).

Data Synthesis and Analysis

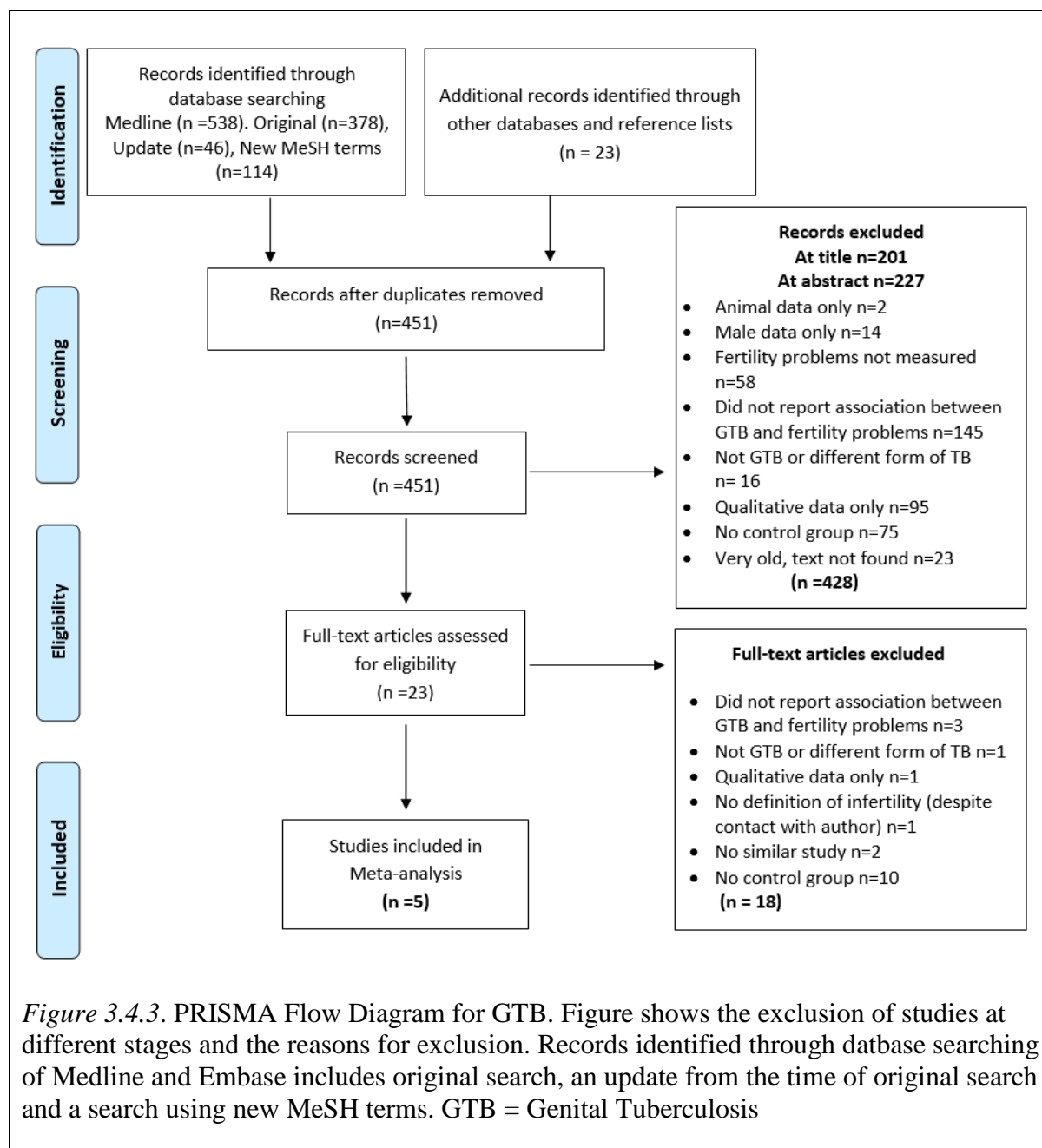
Meta-analyses were computed for the outcomes available in the included studies.

Results

Study Selection

Figure 3.4.3 shows the PRISMA flowchart for number, reason and stage of exclusion of articles. A total of 451 records were identified (after duplicates removed) and most studies

(278 of 451, 61.6%) were excluded because they did not measure ‘fertility problems’, report on the relationship between ‘fertility problems’ and GTB, or did not have a control group. Twenty two articles were excluded because an abstract could not be located despite contact with authors, all of which were published more than 30 years, 18 of 22 were published in the 50s and 60s. Of the 23 full text articles assessed for inclusion five met inclusion criteria and were included in meta-analyses. ‘Fertility problems’ outcomes available in the included studies were: infertility, amenorrhea, primary and secondary infertility. An examination of the impact of GTB on ability to have live birth was not possible due to the lack of primary studies measuring childlessness or rate of live births. In the primary studies, infertility was defined as inability to become pregnant after one year of unprotected sexual intercourse. ‘Amenorrhea’ was defined as not having a period (duration not specified in included studies). The terms ‘primary’ and ‘secondary’ infertility were not well defined in primary studies. Therefore, it could not be ascertained whether these referred to an inability to achieve pregnancy or achieve a live-birth. The most recent definitions of these terms, both refer to an inability to establish clinical pregnancy but the difference between them is that primary infertility refers to a women who has ‘never’ been able to establish clinical pregnancy, while secondary infertility to a women “who has previously been diagnosed with a clinical pregnancy” (Zegers-Hochschild et al., 2017). It was assumed that the definition of primary/secondary used in the study though not reported was applied consistently in the exposed and non-exposed groups.



Characteristics and Design of Included Studies

Table 3.4.2 shows selected sample characteristics of the included studies. Three of the five studies were conducted in India, four included mean age at time of study (30 years old) and one reported participant age in range. Table 3.4.3 shows methodological characteristics of included studies. In all studies cross-sectional data was collected. All samples were

hospital or clinic based and GTB diagnosis was confirmed by histology in all studies but using PCR/culture in only two of the five studies.

Study Quality, Fertility Problems Outcome Measure and Bias

Table 3.4.4 shows the results of quality assessment (see table footnote for criteria). GTB was representative of the population and adequately assessed (confirmed by medical testing or from medical records) in all included studies. The No-GTB group (controls) was well defined and selected from the same population in all studies, but exclusions were adequately reported in three studies. Comparability of at least one confounder in the GTB/No-GTB groups was reported in four of five studies. Matching or adjustment in analysis based on confounders was not performed in any of the studies. 'Fertility problems' outcome was adequately measured in only one of the five included studies, as indicated by blind or independent assessment. Overall the majority of studies (4 of 5) had average quality as per quality assessment.

Numbers reported in Table 3.4.5 indicated higher percentage of infertility, amenorrhea and primary infertility amongst women with GTB than amongst women without GTB. However, secondary infertility was lower amongst women with GTB than amongst women without GTB.

Table 3.4.2.

Sample Characteristics of the Seven Included Studies

Study	Location	Sample (n)	GTB (n)	No-GTB (n)	Age Women ^a		
					GTB	No-GTB	
Ali, 2012	Kassala, Sudan	44 women	25	19	Mean (SD)	34.8 (6.9)	34.7 (7.7)
Bhanothu, 2014	India (south)	302 women	202	100	Mean (SD)	28.54 (4.46)	27.59 (4.62)
Sharma, 2011	India	388 women	99	289	Mean (SD)	28.69 (4.83)	29.72 (9.58)
Malhotra, 2012	India	208 women	104	104	Mean (SD)	28.7 (3.9)	28.2 (3.1)
Kitilla, 2002	Ethiopia	268 women	67	201	Range	Percentage (n)	Percentage (n)
					15-19	0	0.5 (1)
					20-24	19.4 (13)	8.5 (17)
					25-29	38.8 (26)	31.3 (63)
					30-34	29.9 (20)	36.3 (73)
					35-39	11.9 (8)	19.9 (40)
					40-44	0	3.0 (6)
45+	0	0.5 (1)					

Note..^a Age for women at the beginning of the study; GTB = Genital Tuberculosis, SD=Standard deviation; NR= data not reported

Table 3.4.3.

Characteristics of the Design of the Seven Included Studies

	Study design	Data collection	Study period	GTB measure	Infertility outcome measure (duration)
Ali, 2012	Cross-sectional	Maternity Hospital	Jan-Dec 2010	Clinical symptoms and Histology	Infertility defined as failure to become pregnant despite unprotected sexual practice after one year of marriage.
Bhanothu, 2014	Cross-sectional	2 Gynaecology clinics	2006-2014	Clinical symptoms and Histology	Amenorrhea (duration not specified)
Sharma, 2011	Cross-sectional	University Hospital	2007-2010	PCR, Histology, culture, laparoscopy and hysteroscopy	Primary infertility (inability to conceive spontaneously despite one year of regular (3-4 times a week) unprotected intercourse) AND Amenorrhea (duration not specified)
Malhotra, 2012	Cross-sectional	Outpatient Gynaecology clinic	2007-2009	PCR, Histology, culture, laparoscopy and hysteroscopy	Primary infertility Secondary infertility
Kitilla, 2002	Cross-sectional	University Hospital	1995-2000	Surgical and Histology	TFI (tubo-peritoneal) Primary infertility Secondary infertility

Note. PCR = polymerase chain reaction; TFI = tubal factor infertility

Table 3.4.4.

Quality Ratings for the Seven Included Studies on the Basis of an Adapted Newcastle-Ottawa Quality Assessment Scale

	Quality Criterion						Overall rating ^g
	Adequacy of GTB (exposed) measure ^a Max 2 points	Adequacy of control (non-exposed), definition and selection ^b Max 2 points	Comparability of control ^c Max 2 points	Confounders adequately assessed Max 2 points ^d	Adequacy of outcome Infertility measure ^e Max 1 point	None response rate or loss to follow-up ^f Max 1 point	
Ali, 2012	2	2	0	0	0	NA	Average
Bhanothu, 2014	2	2	0	2	1	NA	High
Sharma, 2011	2	1	1	1	0	NA	Average
Malhotra, 2012	2	2	0	1	0	NA	Average
Kitilla, 2002	2	1	0	2	0	NA	Average

Note. ^a GTB was adequately assessed when diagnosis was confirmed by medical testing or hospital records, and it was representative of the cohort i.e. drawn from the same population (up to 2 points); ^b Controls were adequately assessed when selection was comparable to cases, and GTB was excluded properly in the control population (up to 2 points); ^c Comparability of controls was achieved if exposed/non-exposed were matched or adjustment during analysis conducted. One point for rural-urban and one point for any other confounder (up to 2 points); ^d Confounders were adequately assessed if they were obtained from records or a blind interview, and one point was given if the same method was used for both groups (up to 2 points); ^e Infertility outcome was adequately assessed if independent or blind assessment was stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.) (up to 1 point); ^f Point given if same rate for both groups and <20% loss to follow up reported; ^g The overall quality rating was low (0 to 3 points), average (4 to 6 points), or high (7 to 10 points).

Table 3.4.5.

Number and percentage of women with infertility or amenorrhea in the GTB and No-GTB groups in the included studies (k=5)

Outcome		Number of women (%)	
		GTB	No-GTB
Infertility		102/124 (82.3)	127/308 (41.2)
Amenorrhea		24/301 (8.0)	12/389 (3.1)
Type of infertility	Primary	133/171 (77.8)	149/305 (48.9)
	Secondary	38/171 (22.2)	156/305 (51.1)

Note. GTB = genital tuberculosis

Results of Meta-analyses

Three meta-analyses were performed. Figure 3.4.4 displays the first analysis comparing the two studies reporting on ‘percentage infertile’ in women with GTB and those without GTB. This meta-analysis showed a significant pooled effect size (OR 8.91, 95% CI 1.89 to 42.12) and significant heterogeneity ($I^2 = 72\%$, $p = 0.06$). The results indicated that women with GTB were significantly more likely to be infertile (more likely to have fertility problems) than women without GTB.

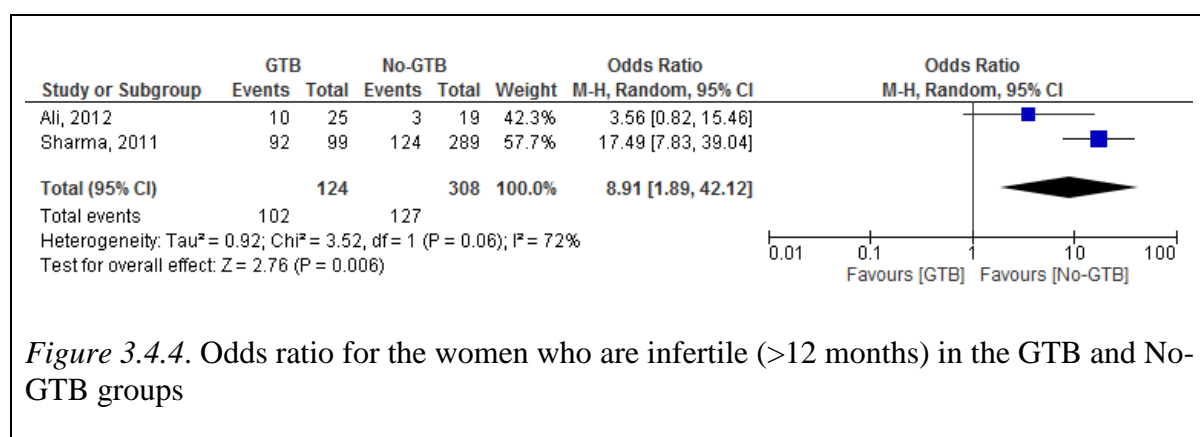


Figure 3.4.5 shows the forest plot and meta-analysis result for the two studies investigating the number of women who have had ‘amenorrhea’. The meta-analysis revealed a significant pooled effect size (OR 4.24, 95% CI 0.23 to 78.14) and significant heterogeneity

($I^2 = 75\%$, $p = 0.05$). The results indicated that the women with GTB were significantly more likely to have ‘amenorrhea’ (more likely to have fertility problems) than the women without GTB.

Heterogeneity could not be explored with sensitivity or subgroup analysis because there was only two studies in the first two meta-analyses.

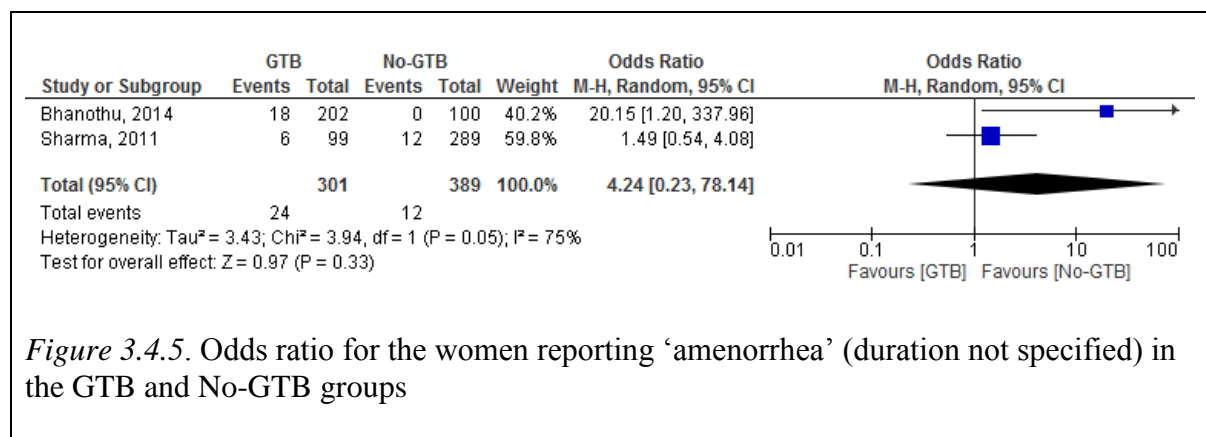
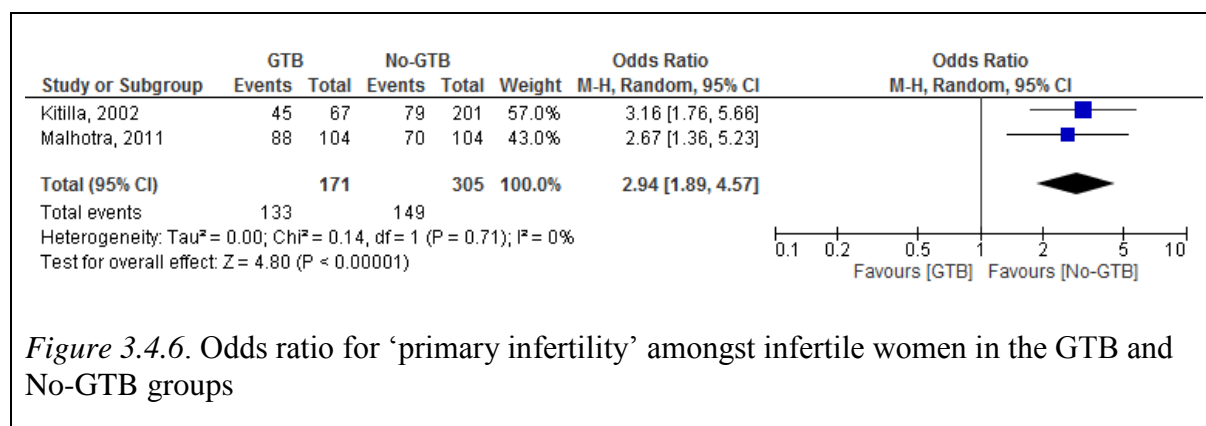


Figure 3.4.6 displays the third analysis comparing two studies reporting on ‘primary infertility’ in infertile women with GTB and those without GTB. The meta-analysis showed a significant pooled effect size (OR 2.94, 95% CI 1.89 to 4.56) and non-significant heterogeneity ($I^2 = 0\%$, $p = 0.71$). The results indicated that in infertile women, those with GTB were significantly more likely to have primary compared to secondary infertility than women without GTB.



Publication bias assessment.

Publication bias was not explored using funnel plots, Eggers test or trim and fill procedures because each analysis included two studies only, thus computation was not possible.

Discussion**Principal Findings**

In the present study the association between GTB and fertility was examined according to the fertility outcomes (infertility, amenorrhea and primary vs. secondary infertility) found in the primary studies. This analytic approach demonstrated that GTB might be a relevant factor for the prediction of ability to become pregnant. A significantly greater number of women exposed to GTB had infertility (more than 12 months) generally and primary infertility specifically, but not amenorrhea. The results of the review lend support to reports in the literature of increased likelihood of infertility and especially primary infertility (Gatongi et al., 2005; Varma, 2008; Ghosh et al., 2011). These findings need to be interpreted in light of methodological considerations (described in detail on pp. 189), such as clinical sampling and the rate of infertility in exposed and control groups. The rate of infertility was higher in the present review compared to population based estimates (Boivin, Bunting, Collins & Nygren, 2007). This indicated that perhaps the sample of women who were included in the primary studies were not representative of the population, therefore the association between infertility and GTB may be exaggerated.

Results indicated that the percentage amenorrhea in women without GTB (3%) was comparable to that in the general population [3-4%] (Pettersson, Fries, & Nillius, 1973; Bachmann & Kemmann, 1982). However, the percentage of amenorrhea in women with GTB (8%) was lower than estimates in other samples of women with GTB [14.3-15%] (Samal et al., 2000; Qureshi et al., 2001).

It can be inferred from these two results combined that the greatly inflated rate of infertility may be independent of amenorrhea, thus suggestive of tubal involvement.

Results indicated that women in the GTB group were more likely to have primary infertility than secondary infertility. The higher rate of primary infertility in the GTB group (77.8%) and the lower rate of secondary infertility (22.2%), found in the current study were corroborated by similar estimates in the literature (Qureshi et al., 2001; Avan et al., 2001). It can be inferred from the higher rate of primary infertility that early onset may be more prevalent in the current samples. Early onset potentially damages the reproductive tract prior to having the opportunity to become pregnant leading to more primary infertility. Late onset manifesting later in the lifespan would have less impact on overall fertility, thus will be underrepresented in clinical samples compared to early onset.

In the present study the effect of GTB on fertility was examined in a set of meta-analyses of observational studies. Although this systematic approach demonstrated that GTB was associated with infertility generally and primary specifically, a causal relationship could not be confirmed, nor could a specific mechanism of action be specified. However, if we apply the 'Bradford Hill criteria' noted in the General Methods (pp. 55), we can see that four of the nine criteria apply to the current review and enhance confidence in the causal relationship between GTB and fertility problems.

The criteria of 'strength' was met because of the large size of the association between GTB and infertility in the current meta-analysis and in primary studies cited in other reviews (see, Gatongi, 2005; Ghosh, 2011; Varma, 2008). The criteria of 'biological plausibility', 'coherence' and 'consistency' were satisfied for GTB due to the molecular level studies that included imaging of lesions (Ahmadi et al., 2014; Chavhan, et al., 2004; Gatongi, 2005; Ghosh et al., 2011; Varma, 2008; Tripathy & Tripathy, 1998) in the female reproductive

tract, bolstering results from observational studies citing high rates of infertility caused by these lesions.

Justification for including GTB in FertiSTAT.

The results would suggest the inclusion of GTB in the adapted FertiSTAT could potentially be justified because it could increase prediction of fertility problems in LMICs. The only observable signs of GTB reported in the literature are menstrual disturbance and/or pelvic pain (Gatongi et al., 2005; Varma, 2008; Ghosh et al., 2011). Since these observable signs and symptoms are included in the current FertiSTAT, GTB might not be an independent factor. However, GTB remains asymptomatic for long periods (Gatongi et al., 2005; Varma, 2008; Ghosh et al., 2011), therefore it might be an independent RF.

In cases where GTB leads to tubal damage and there are no observable signs/symptoms, it remains undiagnosed until a woman is unable to become pregnant in which case it is diagnosed during routine infertility investigations (Gatongi et al., 2003; Varma, 2008; Ghosh et al., 2011). The woman would then be informed of the impact of GTB on fertility, reducing the utility of the FertiSTAT. If the inclusion of GTB is not found to increase the predictive ability of the tool, the wording of the 'painful periods' item could be modified, to incorporate pain from GTB that does not only occur during menstruation as the only observable sign of the disease.

Implications for Practice

Awareness of the risks associated with GTB highlighting its silent nature should be communicated to couples. Women who are at higher risk of contracting GTB (living in a region with high prevalence of TB, family member with TB) should be made aware of how GTB can affect their reproductive tract. Policy makers and healthcare workers can also utilize results when developing and implementing comprehensive pre-pregnancy care

packages that should include GTB screening. To the authors knowledge, GTB has not been included in any preconception package, but TB was reported as one of the preconception risk factors examined in “The Dutch national summit on preconception care” (2015). Healthcare practitioners in countries with high prevalence of TB should be informed of the potential impact of GTB and to the latent nature of the disease, which makes it pertinent to include GTB screening as part of a routine pre-pregnancy examination. Menstrual disturbances and/or pelvic pain should alert practitioners to test for GTB, to enable early detection before irreversible damage to the reproductive tract occurs.

Strength and Limitations in Included Studies

The heterogeneity in study methodology and outcome measures in included studies could affect the comparability of these studies and the generalizability of the results. Heterogeneity in GTB measure (different diagnostic tests), ‘fertility problems’ outcome (different duration of amenorrhea, different definition of primary or secondary infertility) and data collection methods (examinations and records), can affect the practical applicability of the results. Subgroup analysis could not be performed because there were too few studies. However, future research should endeavour to reduce heterogeneity by applying comparable methods (design and data collection), using best practice for diagnostic testing of GTB (at least culture, but preferably PCR) and by applying similar well defined outcomes e.g. 12 months of inability to become pregnant. The quality of each study independently did not appear to affect the overall results of the review since the majority of studies were of average quality.

Another limitation of the primary studies was the exaggerated estimates of infertility in both the GTB and no GTB groups. In the current sample the rate of infertility in the No-GTB group was 41.2% compared with a maximum population estimate of 15% (Boivin, et

al., 2007). Additionally, the rate of infertility in the GTB group (82.3%) was also higher than in GTB samples, approximately 50% (range 10-85%) see Table 3.4.1. The inflation in common can be explained by clinical sampling but the exaggerated infertility in the GTB group that is beyond that seen in the No-GTB group could be due to other reasons. First, the women in the GTB group that were presenting for treatment have become symptomatic (pelvic pain, infertility, amenorrhea etc.), indicative of severe disease. Second, the main presenting concern for care in women with GTB is the inability to become pregnant, see Table 3.4.1. Furthermore, the difference between the rate of infertility in the GTB sample in the current study and other clinical samples of GTB can be attributed to issues such as presentation time (how long women wait to seek help), the type of clinics sampled (general, gynaecological, infertility), whether the sample was rural or urban and other economic and environmental barriers to help seeking. In the 'prevalence of infertility' meta-analysis, two studies were included, the rate of infertility was within the expected range in one of them (Ali, et al., 2012) [40%] but higher in the other one (Sharma et al., 2011) [92%]. In the Sharma et al., (2011) study the sample was from women presenting for hysteroscopy, and infertility is recognized as one of the main presenting complaints that warrants hysteroscopy (NHS Choices, Hysteroscopy, 2016). Therefore, it can be inferred that the inflated estimate reflects a difference in presentation for treatment and sampling. However, this does not negate the fact that there was a significant difference that could be indicative of the damage caused by lesions in the reproductive tract that hinders ability to become pregnant.

Bias relating to the primary studies included selection bias, information bias and bias due to confounding. The selection of participants based on hospital attendance can inflate the rate of infertility because infertility is the presenting complaint, as was indicated previously. However, the selection of participants was from the same sample and information was gathered using the same method for both the exposed and non-exposed groups in all the

studies. Therefore, it can be assumed that selection and information bias may not affect results considerably, but care must be taken when generalizing the results of this review. Bias due to confounder is a major limitation of the studies included, because matching the groups for confounders or including confounders in the analysis was not reported in any of the included studies. The most important confounder, whether the participant was in a rural or urban setting was only reported in three studies. This is an important confounder because people living in urban areas (especially in poverty) tend to live in overcrowded residencies, which is linked to an increase in the likelihood of contracting TB (Schmidt, 2008; Baker, Das, Venugopal, & Howden-Chapman, 2008). Since overcrowding may not be reported separately or quantified appropriately, rural-urban living was taken as a proxy variable because it is closely correlated to overcrowding. In general urbanization leads to increased population density, overcrowding and more mobility among migrants seeking employment all of which impact the transmission of TB (Schmidt, 2008). The WHO reported that the link between poverty and TB is intermediated by factors such as poorly ventilated housing, overcrowding, smoking, malnutrition, stress, social deprivation and poor social capital, thus it would be important to consider all these factors (Figueroa-Munoz & Ramon-Pardo, 2008). There could have been an unequal distribution of other confounders (smoking, SES, education, access to healthcare) in the exposed and non-exposed groups, which might have influenced the relationship between GTB and ‘fertility problems’.

Another limitation relating to the primary studies is the use of observational designs. As discussed in previous chapters observational designs are prone to biases, such as sampling bias that can invalidate results. However randomization would not have been possible or ethical for GTB. This review comprised of five cross-sectional studies that can be a good starting point to identify associations but should be followed by more rigorous studies with a cohort design (Mann, 2003) as explained in the next section.

Future Research

Since RCTs producing GTB would be unethical, future research to disentangle the effect of GTB on fertility problems would require prospective cohort studies, failing that retrospective cohort studies (Mann, 2003). RCTs that examine risk of infertility in treated/untreated samples of GTB could also be examined. Researchers should investigate the causal mechanisms involved in GTB, the impact of severity of the disease, which parts of the reproductive tract are affected, the differential impact on primary versus secondary infertility and the specific reasons for the increased prevalence of amenorrhea. Ideally, large population-based prospective cohort studies following women who are at increased risk of TB should be conducted to assess true rates of consequences such as infertility and amenorrhea. Additionally, household survey where identified women are then referred for treatment can be conducted. This survey can also compare women who have been vaccinated versus those who have not been vaccinated (by visually confirming through scare). The inclusion of control groups matched for confounders such as rural-urban living, overcrowding, poorly ventilated housing, SES, smoking, malnutrition, age, access to healthcare and education, should be included by matching the groups or in multivariate analysis. Realistically, prospective studies may not be ethical because once detected GTB or TB should be treated with antibiotics to prevent further disease progression, thus retrospective cohort studies may be the best option.

Conclusion

Fertility problems including infertility generally and primary infertility specifically as well as amenorrhea have been reported as negative consequence of GTB in the literature but evidence to support these claims has been fraught with limitations such as lack of control and sampling infertile women only. Results of the current meta-analyses confirmed reports

in the literature that GTB was association with an inability to become pregnant. Therefore, inclusion of GTB in the adapted FertiSTAT could potentially increase the predictive ability of the tool. It is important to note that this area of research should be re-examined due to the methodological shortcoming of primary studies and the small number of included studies in the meta-analyses. The fertility implications of GTB should be communicated to women at risk for contracting GTB.

Study 3.5: Systematic Review and Meta-analysis of Observational Studies Examining the Association of Bacterial Vaginosis and Fertility Problems

Introduction

Bacterial Vaginosis (BV) was one of the risk factors identified through the process of adapting the FertiSTAT and was endorsed by the experts in Study 2.1 (Chapter 2, pp. 25). The validity of this risk factor as a predictor of fertility problems was examined in the current systematic review using the operational definitions of fertility problems and risk factor applied in the original development of FertiSTAT (Bunting & Boivin, 2010).

Description of BV

BV is an infection of the lower female reproductive tract that is characterized by an imbalance in the naturally occurring microorganisms of the vagina (Mastromariano, et al., 2014; Money, 2005). The imbalance is typically a depletion of normal lactobacillus and an overgrowth of anaerobes (Viniker, 1999). In healthy women lactobacilli are the dominant bacteria, there are small numbers of other bacteria, and the pH is retained below 4.5. The acidic environment provides protection from infection (Viniker, 1999). In BV the pH of the vagina becomes less acidic and can be elevated up to 6.0, lactobacilli are reduced in number and the flora is dominated by an overgrowth of anaerobic bacteria (up to a thousand-fold more than normal). This imbalance renders the genital tract at increased risk of an overgrowth of harmful bacteria (endogenous to the vagina) and more susceptible to exogenous infections such as STIs and HIV (Mastromariano, 2014; Money, 2005; Morris, Nicoll, Simms, Wilson & Catchpole, 2001; Allsworth & Peipert, 2007).

According to the UK National Guideline for the management of Bacterial Vaginosis (Hay, Patel & Daniels, 2012), BV is the most common cause of abnormal vaginal discharge

in women of childbearing age. BV can present with various symptoms including vaginal discharge that is grey, yellow, odorous, abdominal pain, intermenstrual bleeding or prolonged menses (Morris, et al., 2001). The discharge may also be thin, white and homogenous (Hay, et al., 2012), with no signs of inflammation and up to 50% of cases may be asymptomatic (Hay, et al., 2012; Woodrow & Lamont, 1998). BV can be treated with antibiotics but reoccurrence is common (Hay, et al., 2012; Morris, et al., 2001; Money, 2005). A meta-analysis of 43 observational studies reporting on BV and sexual behaviour has shown an increased susceptibility to BV linked to change of sexual partner, but was not shown to be independently related (Fethers, Fairley, Hocking, Gurrin & Bradshaw, 2008). BV has also been found to be associated with vaginal douching (Brotman, et al., 2008), use of intrauterine device (Avonts, et al., 1999; Shoubnikova, Hellberg, Nilsson & Mardh, 1997), black race (Hay, et al., 1994; Goldeberg, et al., 1996; Llahi-Camp, Rai, Ison, Regan & Taylor-Robinson, 1996) and smoking (Hay, et al., 1994; Llahi-Camp, et al., 1996; Jonsson, Karlsson, Rylander, Gustavsson & Wadell, 1997; Rahm, Odling & Pettersson, 1991). Change of sexual partners and an increased number of sexual partners has been reported in some studies as a risk for developing BV (Hay, et al., 2012; Morris, et al., 2001, Money, 2005). However, BV is not classified as a sexually transmitted infection (STI) due to a lack of unequivocal evidence because the exact molecular level understanding is not complete (Hay, et al., 2012; Morris, et al., 2001, Money, 2005) and because it has been reported in virgins (Bump & Buesching, 1988; Papanikolaou, Tsanadis, Dalkalitsis & Lolis, 2002).

Since BV is not caused by an infection from an external organism, rather it is an imbalance of existing vaginal microorganisms, its diagnosis has been problematic because culture of vaginal swab can be positive even for women without BV i.e. false positive (Money, 2005; Hillier, 1993). There are currently two mechanisms for the diagnosis of BV: using clinical criteria of which the Amsel's criteria (Amsel, et al. 1983; Money, 2005) are the

most widely accepted, or using laboratory-based testing, gram stain method using the Nugent scoring system (Nugent, Krohn, & Hillier, 1991). The gram stain method using Nugent scoring is currently the gold standard for the diagnosis of BV (Money, 2005; Mohammadzadeh, Dolatian, Jorjani & Majd, 2015), see Table 3.5.1. Although there is debate as to whether the Amsel criteria are as good as the Nugent test, it is noted in the literature that when lab equipment is not present the Amsel criteria is a good substitute for the Nugent test (Money, 2005; Mohammadzadeh, et al., 2015).

Table 3.5.1.

Clinical and Laboratory Approaches, Criteria and Evaluation for the Diagnosis of Bacterial Vaginosis

Approach	Criteria	Evaluation
Amsel criteria (clinical)	(1) Thin, white, homogeneous discharge (2) Clue cells on microscopy of wet mount 5 (3) pH of vaginal fluid >4.5 (4) Release of a fishy odour on adding alkali (10% KOH)	At least three of the four criteria are present for the diagnosis to be confirmed
Gram stained vaginal smear (laboratory)	Grade 1 (Normal): Lactobacillus morphotypes predominate Grade 2 (Intermediate): Mixed flora with some Lactobacilli present, but Gardnerella or Mobiluncus morphotypes also present Grade 3 (BV): Predominantly Gardnerella and/or Mobiluncus morphotypes. Few or absent Lactobacilli	To be evaluated with the Nugent criteria or the Hay/Ison criteria

Note. BV = bacterial vaginosis; UK guidelines for the management of BV (Hay, Patel & Daniels, 2012)

The prevalence of BV varies wildly depending on the population sampled. It has been reported to be as high as 50.9% in rural Uganda (Paxton, 1998), 35% of women attending STI clinics (Eschenbach, 1993), 29.2% of women ages 14–49 in a nationally representative sample in the US (Koumans, et al., 2007), 29% of non-institutionalized American women (Allsworth & Peipert, 2007), 24.6% of women undergoing IVF (Ralph, Rutherford & Wilson, 1999) and as low as 10-20% of unselected population (Mead, 1993). The prevalence of BV in pregnant women also varies with the highest percentage reported being 32.5% of pregnant inner city American women (McGregor, et al.,

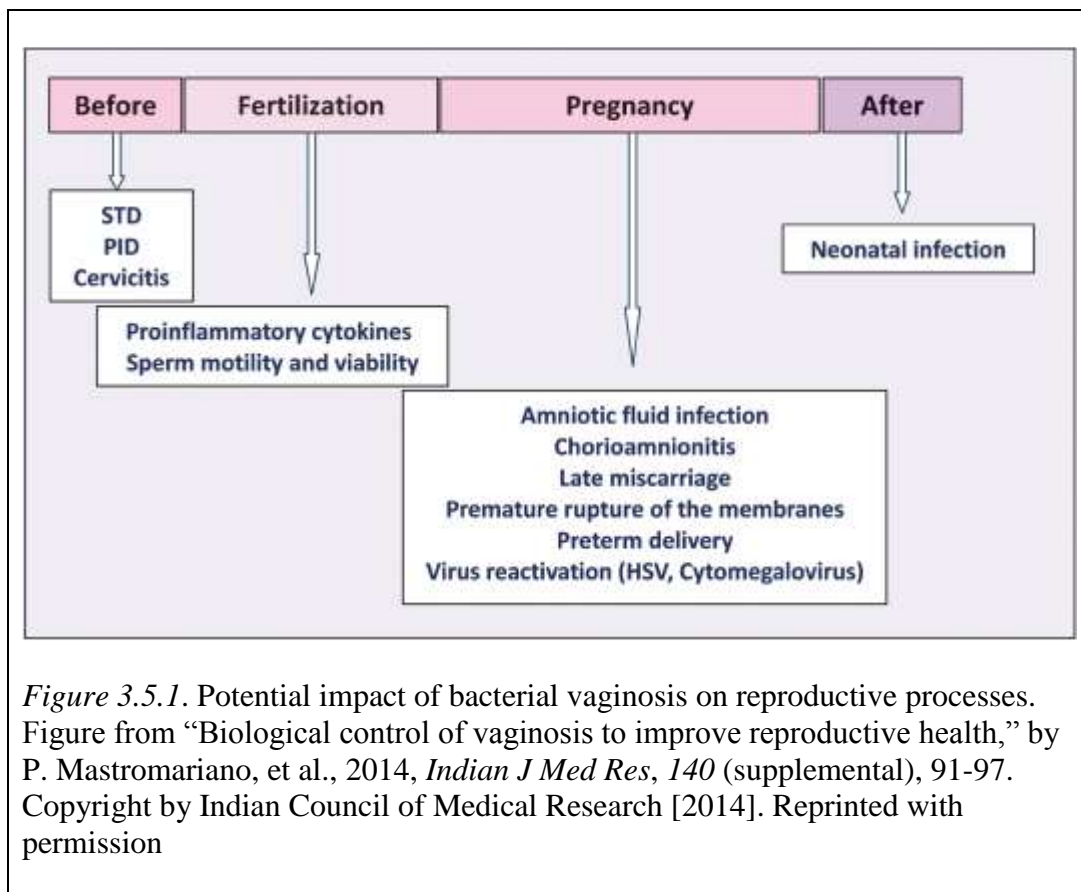
1995), 28% of women undergoing pregnancy termination in the UK (Blackwell, Thomas, Wareham & Emery, 1993), 15-20% of pregnant women (Eschenbach, 1993) and as low as 8.6% by Nugent's method in a sample of pregnant women in rural India (Dadhwal, Hariprasad, Mittal, S. & Kapil, 2010).

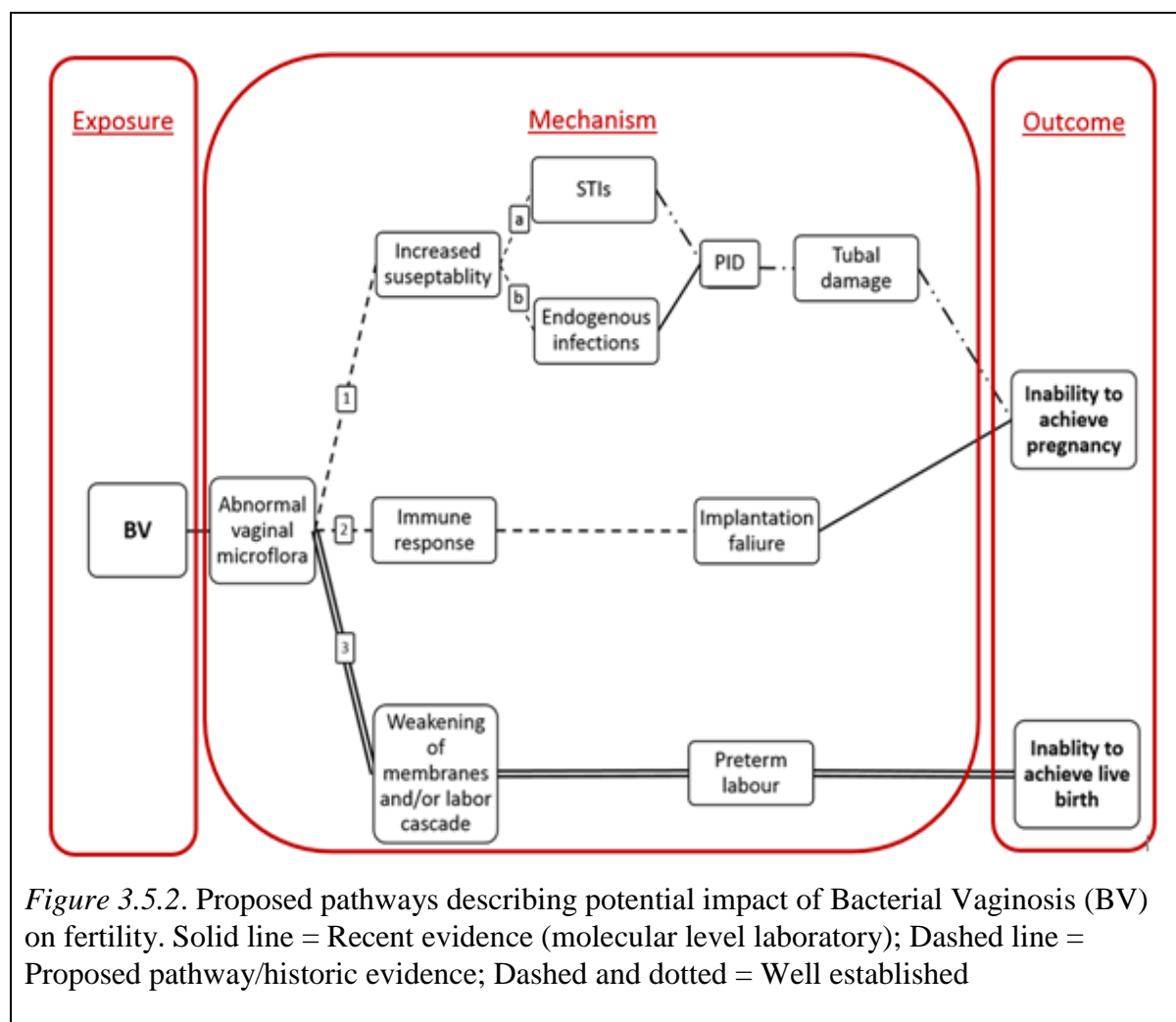
Plausible Mechanisms to Explain why BV Could be Associated with Fertility Problems

An examination of the potential relationship between BV and infertility requires an understanding of PID. Authors of the UK guidelines for the management of PID indicated that infection ascending to the upper reproductive tract can cause inflammation of the different parts of the tract e.g. endometritis (endometrium), salpingitis (fallopian tubes) etc. (Ross & McCarthy, 2011). This inflammation of the reproductive tract is collectively known as PID. Infectious agents known to ascend through the vagina include exogenous bacteria like *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Mycoplasma genitalium* and endogenous anaerobic bacteria like *Prevotella*, *Atopobium* and *Leptotrichia*. The authors indicated that infertility is one of the consequences of PID and that the risk of developing infertility increases in cases of delayed treatment and repeated episodes (Ross & McCarthy, 2011). The WHO estimates that 40% of women with untreated gonorrhoea or chlamydia will develop PID and that 25% of women with PID will develop infertility (WHO, 2007, Global strategy for the prevention and control of sexually transmitted infections: 2006–2015).

The relationship between BV and reproductive processes has been reported in the literature and several attempts to explain the mechanism of action have been reported, see for example Figure 3.5.1. One pathway suggested in the literature was via increased susceptibility to infections (exogenous or endogenous) that lead to PID and consequently tubal damage (Mastromariano, et al., 2014), see Figure 3.5.2. A second pathway proposed that the overgrowth of endogenous microflora triggered an immune response which consequently hindered implantation (Hay, 2004; Hay, Patel & Daniels, 2012; Hillier et al.,

1996; Korn, et al., 1995; Mastromariano, et al., 2014; Sweet, et al., 1987), see Figure 3.5.2. In addition to pathways that show the potential impact of BV on preimplantation and fertilization processes, there is a third pathway that helps explain the impact of BV on adverse pregnancy related outcomes and the consequent inability to have a live birth, see Figure 3.5.2.





In the first pathway, the absence of vaginal lactobacilli characteristic of BV, renders the vagina more susceptible to external bacteria like *Nesseria gonorrhoeae* and *Chlamydia trachomatis* (Wiesenfeld, Hillier, Krohn, Landers & Sweet, 2003), and viral infections such as HIV, HPV and herpes simplex virus (Martin, et al., 1999; Cherpes, Meyn, Krohn, Lurie & Hillier, 2003). These harmful microorganisms can increase incidence of PID and consequently lead to TFI (Mastromariano, et al., 2014; Ross & McCarthy, 2011; WHO, 2007, Global strategy for the prevention and control of sexually transmitted infections), proposed 'Pathway 1(a)' in Figure 3.5.2.

The absence of vaginal lactobacilli can also lead to an overgrowth of endogenous bacteria. Evidence for the involvement of an overgrowth of endogenous microflora comes from laboratory findings confirming that BV microflora ascend from the vagina to the uterus and the fallopian tubes (Hillier et al., 1996; Korn, et al., 1995; Sweet, et al., 1987). These studies reported laboratory findings confirming the presence of BV related bacteria in the endometrium and fallopian tubes of women with PID, more endometritis in symptomatic BV women and more BV microflora in the endometria of women with endometritis (Hillier et al., 1996). These studies provide evidence for ‘Pathway 1(b)’ in Figure 3.5.2. In the second pathway it is proposed that endometritis due to BV could affect the implantation of the embryo and placenta, independent of tubal involvement (Hay et al., 2004; Mastromariano, et al., 2014; Hay, 2004), see Figure 3.5.2. A positive association between lactobacilli and live birth rate was demonstrated in women undergoing IVF in the US and the authors indicated that the lactobacilli create an environment in the endometrium that is favourable for implantation and placentation (Eckert, Moore, Patton, Agnew & Eschenbach, 2003). When lactobacilli are absent, normal microflora become pathogenic, which results in an immune response (production of proinflammatory cytokines) that alters the balance of immune cells (T-helper cells) and this imbalance can then result in failure of implantation (Moore, de Waal Malefyt, Coffman & O’Garra, 2001). In another study on women undergoing IVF, authors found that BV was associated with raised levels of mediators of immunity (interleukin-1b and interleukin-8 cytokines) in the cervix (Spandorfer, Neuer, Giraldo, Rosenwaks & Witkin, 2001). The authors also reported that there were no significant differences in outcome of IVF; however, detecting lactobacilli on the catheter tip after implantation of the embryo was associated with high rate of success in IVF (Eckert, et al., 2003). These studies suggest that the diminished lactobacilli levels result in bacterial overgrowth that triggers an immune response that could ultimately hinder implantation, supporting ‘Pathway 2’ in Figure 3.5.2.

The suggested mechanism of action in the third pathway for the effect of BV on preterm labour involves the release of cytokines and prostaglandins that initiate labour that is triggered prematurely by the toxins produced by the BV microflora (McDonald, O'Loughlin, Vigneswaran, Jolley, Harvey & McDonald, 1997; Morris, et al., 2001). Preterm labour can also be triggered by the release of enzymes (sialidases and mucinases) by bacteria, allowing penetration of mucus and weakening of the membranes (Howe, et al., 1999; McGregor, et al., 1994). Cases where preterm labour was due to chorioamnionitis (an infection of the foetal membranes) were found to be related to organisms associated with BV identified in the membranes more often than any other putative infective agent (Hillier, et al., 1988; Heller, Moorehouse-Moore, Skurnick & Baergen, 2003; Goldenberg, Hauth & Andrews, 2000; Sebire, 2001). This evidence suggests that the BV microflora release chemicals that affect the membranes or initiate the natural labour cascade, in both cases leading to preterm birth.

Reproductive Health Consequences of BV

The negative impact of BV on women's reproductive health and specifically fertility problems has been reported in the literature. A summary of the consequences in the reviewed literature is presented in Table 3.5.2. The reviews summarized were subjected to quality evaluation using the "Critical Appraisal of Systematic Reviews" published by the WHO (Abalos, Carroli, Mackey & Bergel, 2001).

Morris et al. (2001) conducted a narrative review of the literature on the prevalence of BV, associated factors, consequences and interventions. The search was limited to English language publications since 1984 on both Medline and the Cochrane database. The authors noted that BV was associated with considerable morbidity in women of reproductive age, however, they noted that the majority of the studies investigating the consequences of BV include in their review were cross-sectional, restricting the inference of a causal relationship. The authors reported the following consequences: preterm delivery, miscarriage, pelvic

inflammatory disease (PID), tubal factor infertility (TFI), cervical intraepithelial neoplasia (CIN) and increased susceptibility to STIs, HIV and human papilloma virus (HPV), see Table 3.5.2. Morris et al. (2001) noted that the association between BV and preterm delivery has been well established, but there is not yet enough evidence to establish a concrete association for other consequences like PID, TFI and first trimester miscarriage. The authors suggested that the biological similarity in vaginal microflora in BV and PID in the absence of STIs makes the association between BV and PID and the progression from BV to PID biologically plausible (Morris, et al., 2001).

Hay (2004) reviewed the literature to summarize knowledge on the relationship between BV and miscarriage. The author did not report on methods of the review process, but presented a summary of the possible mechanism of action of BV on negative pregnancy outcomes including first and second trimester loss, see Table 3.5.2 for studies included. The author noted the following consequences: adverse pregnancy outcomes e.g. preterm delivery and second trimester loss, and negative IVF outcomes e.g. first trimester loss. The author reported that the risk of miscarriage and preterm labour persists even when BV resolves during pregnancy (Hay, 2004). The evidence in the Hay (2004) review was supported by two subsequent reviews (McDonald, et al, 2007; Brocklehurst, Gordon, Heatley & Milan, 2013). Evidence from these reviews indicated that if treatment of BV occurred before 20 weeks gestation treatment could reduce the risk of preterm birth, but only if the group of women with BV included those with abnormal microflora categorized as intermediate flora (McDonald, et al, 2007; Brocklehurst et al, 2013). Treatment was also beneficial in women who had a history of preterm birth (McDonald, et al, 2007; Brocklehurst et al, 2013). Hay (2004) also noted that studies examining types of infertility and BV in women undergoing IVF reported significantly more BV in women with TFI and anovulation than, male factor, endometriosis and unexplained infertility, see Table 3.5.2.

Table 3.5.2.

Summary of Reproductive Health Consequences of Bacterial Vaginosis Reported in the Literature

Reproductive outcome	Effect of BV	Primary study	Statistics reported	Review
Preterm labour/delivery	Women with BV at increased risk of preterm birth	Hillier, et al., 1995	ORs between 1.8 and 6.9	Hay, (2004)
		McGregor, et al., 1995 Hay, et al., 1994 Hillier, et al. 1995 Hauth, Goldenberg, Andrews, DuBard & Copper, 2001	Attributable risks between 2-10 for BV in pregnancy leading to preterm delivery (women with no previous history) and over 30 (women with a history of a previous preterm birth)	Hay, (2004) Hay, et al., (2012) Morris et al., (2001)
	The strong association between BV and loss before 20 weeks was confirmed in women examined at less than 14 weeks' gestation (Belgium)	Donders, et al., 2000	RR= 5.4	Hay, (2004)
	The overall risk of preterm birth for women with BV was determined in meta-analysis of 20 232 pregnancies	Leitich, et al., 2003	Studies that screened before 16 weeks' gestation OR= 7.55, Studies that screened before 20 weeks gestation OR= 4.20	Hay, (2004)
	Preterm labour due to chorioamnionitis found to be related to organisms associated with BV	Hillier, et al., 1988 Heller, Moorehouse-Moore, Skurnick & Baergen, 2003 Sebire, 2001 Goldenberg, Hauth & Andrews, 2000	NR	Hay, (2004) Hay, et al., (2012)
	Release of enzymes by bacteria, allowing penetration of mucus and weakening of the membranes, leading to preterm labour Alterations in vaginal microbiology associated with late miscarriage and premature birth	Howe, et al., 1999 Koumans, Markowitz & Hogan, 2002	NR NR	Hay, (2004) Mastromarino, et al., (2014)
Miscarriage	Higher risk for preclinical pregnancy loss in women who had BV than those who didn't (conceived by IVF)	van Oostrum, et al., (2013) Meta-analysis	(OR 2.36, 95% CI 1.24 to 4.51).	van Oostrum, et al., (2013)
	Even if BV resolves during pregnancy, that doesn't reduce risk of miscarriage and preterm labour	Riduan, et al., 1993 Lamont, Duncan, Mandal & Bassett, 2003	NR	Hay, (2004)
	More first trimester miscarriage in women with BV in a sample of women who conceived with IVF treatment, even after adjusting for factors known to increase risk of miscarriage	Ralph, Rutherford & Wilson, 1999	First trimester miscarriage was 31.6% for those with BV compared with 18.5% for those with normal vaginal flora (crude odds ratio 2.49, 1.21 to 5.12)	Hay, (2004) Morris et al., (2001)
	In study on natural conception BV was associated with miscarriage early in the second trimester 13-15 weeks, but not at 10-12 weeks	Oakeshott, et al., 2002	13-15 weeks' gestation (OR 3.5; 1.2-10.3) 10 and 12 weeks gestation (OR 1.32; 0.67-2.62)	Hay, (2004)

Reproductive outcome	Effect of BV	Primary study	Statistics reported	Review
PID	BV found to be more common in women with PID.	Moi, 1990 Taylor, 1997 Soper, Brockwell, Dalton & Johnson, 1994 Larsson, Platz-Christensen, Thejls, Forsum & Pahlson, 1992	NR	Morris, et al., (2001) Hay, et al., (2012)
	BV related organisms have been isolated from the endometrium and fallopian tubes of women with PID	Sweet, 1987	NR	Hay, (2004)
	Increased risk of PID in women with BV (using only clinical diagnosis for PID)	Eschenbach, et al., 1988	Nine-fold	Morris, et al., (2001)
	Increased risk of PID in women with BV (using gold standard laparoscopy to diagnose PID)	Peipert, Montagno, Cooper & Sung, 1997	Three-fold	Morris, et al., (2001)
	BV associated with a markedly increased risk for development of PID	Ness, et al., 2005	NR	Hay, et al., (2012)
Endometritis	Endometritis more in women with BV than without	Hillier, et al., 1996	(OR 15, 95% CI 2-686)	Morris, et al., (2001)
	Microorganisms associated with BV were isolated more from the endometria of women with than without plasma cell endometritis	Korn, et al., 1995	(OR 12.4)	Morris, et al., (2001) Hay, (2004)
	BV associated with post-partum endometritis	Watts, Krohn, Hillier & Eschenbach, 1990	NR	Hay, et al., (2012)
Infertility	Significantly more BV in women attending infertility clinic than attending antenatal clinic	van Oostrum, 2013 Meta-analysis	(OR 3.32, 95% CI 1.53 to 7.20)	van Oostrum, et al., (2013)
	In women undergoing IVF more BV in women with TFI than those with non-TFI	Gaudoin, Rekha, Morris, Lynch & Acharya, 1999 Liversedge, et al., 1999 van Oostrum, et al., (2013)	NR	Morris, et al., (2001)
	Preclinical pregnancy loss following IVF higher in infertility patients with BV than those with no BV	van Oostrum, et al., (2013)	(OR 2.36, 95% CI 1.24 to 4.51).	van Oostrum, et al., (2013)
	BV more common in women with TFI than other types of infertility in sample of women undergoing IVF	Liversedge, et al., 1999	BV more common in women with TFI (31.5%) than non-TFI (19.7%) infertility (OR 1.87)	Hay, (2004)
		Wilson, Ralph & Rutherford, 2000.	Compared with endometriosis (OR 3.63, 95% CI 1.52–8.67), male factor (OR 2.98, 95% CI 1.80–4.90), and unexplained infertility (OR 2.20, 95% CI 1.35–3.59) [adjusted ORs]	Morris, et al., (2001) Hay, (2004)
	Significantly more BV in women with TFI as compared to other causes of infertility in sample of women undergoing IVF	van Oostrum, et al., (2013)	(OR 2.77, 95% CI 1.62 to 4.75)	van Oostrum, et al., (2013)
	Significantly more BV in women with anovulation than other types of infertility (but less than TFI) in sample of women undergoing IVF	Wilson, Ralph & Rutherford, 2000.	Compared with endometriosis (OR 3.77, 95% CI 1.28–11.08), male factor (OR 3.09, 95% CI 1.37–6.96), and unexplained infertility (OR 2.29, 95% CI 1.02–5.12) [adjusted ORs]	Morris, et al., (2001) Hay, (2004)
A correlation between bacterial vaginosis, immune response and idiopathic infertility demonstrated in sample of women undergoing IVF	Spandorfer, Neuer, Giraldo, Rosenwaks & Witkin, 2001	NR	Mastromariano, et al., (2014)	

Reproductive outcome	Effect of BV	Primary study	Statistics reported	Review
Increased susceptibility to infections	More HIV+ in women with severe BV (score of 9-10 on a Gram stain) than those with normal vaginal flora in Uganda	Wawer, et al., 1999 Sewankambo, et al., 1997	(OR 2.08, 95% CI 1.48-2.94)	Morris, et al., (2001)
	Women with BV significantly more likely to seroconvert before giving birth and after giving birth (Malawi)	Taha et al., 1998	(OR 3.7, P = 0.03) before giving birth (OR 2.3, P = 0.04) after giving birth	Morris, et al., (2001) Hay, et al., (2012)
	Women with abnormal flora on Gram's stain at increased risk of HIV acquisition (Kenya)	Martin, et al., 1999	(HR = 1.9, 95% CI 1.1-3.1)	Morris, et al., (2001)
	Absence of lactobacilli, characteristic of BV and associated with an increased risk of HIV	Martin, et al., 1999	(HR = 2.0; 95% CI 1.2-3.5)	Morris, et al., (2001) Mastromariano, et al., (2014)
	Pregnant women with abnormal vaginal flora at increased risk of HIV seroconversion (North Carolina, USA)	Royce, Thorp, Granados & Savitz, 1999	(RR 4.0, 95% CI 1.1-14.9)	Morris, et al., (2001)
	BV is associated with a markedly increased risk for acquisition of HIV	Cu-Uvin, et al., 2001 Schwebke, 2003 Atashili, Poole, Ndumbe, Adimora & Smith, 2008	NR	Hay, et al., (2012)
	BV risk factor for female to male HIV transmission	Cohen, et al., 2012	adjusted OR (3.06, 1.35-6.95)	Hay, et al., (2012)
	BV associated with a markedly increased risk for acquisition STIs	Martin, et al., 1999 Cherpes, Meyn, Krohn, Lurie & Hillier, 2003 Harmanli, Cheng, Nyirjesy, Chatwani & Gaughan, 2000	NR	Mastromariano, et al., (2014)
	Abnormal vaginal flora lacking lactobacilli facilitates infection by parasites e.g. Trichomonas vaginalis and bacteria e.g. Neisseria gonorrhoea and Chlamydia trachomatis	Wiesenfeld, Hillier, Krohn, Landers & Sweet, 2003	NR	Mastromariano, et al., (2014)
	Absence of vaginal lactobacilli, is an independent risk factor for acquisition of herpes simplex virus	Cherpes, Meyn, Krohn, Lurie & Hillier, 2003	NR	Mastromariano, et al., (2014)
Cervical intraepithelial neoplasia (changes in the squamous cells of the cervix.)	Association between BV and CIN (suggested to be caused by nitrosamines produced by the abnormal vaginal microflora)	Hudson, Tidy, McCulloch & Rogstad, 1997 Pavic, 1984	NR	Morris, et al., (2001)
	Significantly more BV in women with CIN	Uthayakumar, Boyle, Barton, Nayagam & Smith, 1998	NR	Morris, et al., (2001)

Note: BV = bacterial vaginosis; OR = odds ratio; RR = risk ratio; NR = not reported; IVF = in vitro fertilization; PID = pelvic inflammatory disease; TFI = tubal factor infertility; HIV = human immunodeficiency virus; STIs=sexually transmitted infections; CIN = Cervical intraepithelial neoplasia

Hay et al. (2012) conducted a review as bases for the UK guidelines for the management of BV that included a search of Medline, Embase, Centers for Disease Control and prevention (CDC) STD Treatment Guidelines, European (IUSTI/WHO) Guidelines and Cochrane Databases. Articles were evaluated and recommendations provided and categorized according to best available evidence (Hay, Patel & Daniels, 2012). The authors reported the

following as potential complications of BV: increased risk of acquisition of HIV in pregnant women, increased prevalence of BV in women with PID, late miscarriage, preterm delivery, preterm premature rupture of membranes, and postpartum endometritis (Hay et al., 2012), see Table 3.5.2.

In a narrative review of the literature, Mastromariano, et al. (2014), reported on the effect of BV on reproductive processes in women and men. The authors noted consequences such as increased susceptibility to STDs, PID and other infections, complications during pregnancy e.g. late miscarriage and preterm delivery, and neonatal infections. Although this review covered a wide range of literature and areas where BV has been shown to have an impact, the authors did not report search methodology, and pooled estimates were not calculated.

Van Oostrum and colleagues (2013) conducted a systematic review and meta-analysis to assess the association of BV with the cause of infertility in women in general and the effect on conception rates and early pregnancy losses in women undergoing IVF specifically (van Oostrum, Sutter, Meys & Verstraelen, 2013). The authors reported that BV was significantly more prevalent in women attending infertility clinics than antenatal clinics (OR 3.32, 95% CI 1.53 to 7.20), significantly more prevalent in women with TFI as compared to other causes of infertility in samples of women undergoing IVF (OR 2.77, 95% CI 1.62 to 4.75) and associated with higher risk of preclinical pregnancy loss, following IVF (OR 2.36, 95% CI 1.24 to 4.51). The authors reported that BV was not significantly associated with decreased conception rates, or elevated risk of first trimester miscarriage, in women who had conceived by IVF. The methodology of this review was high as gauged by “Critical Appraisal of Systematic Reviews” (Abalos, et al., 2001). However, there are methodological issues with the representativeness of the samples included in this review that could potentially limit generalizations that can be made. First, there were four studies that were published before the review that were not included in the review and meta-analysis. Second, more than half (7 of

12, 58%) of the included studies were reporting on the prevalence of BV in infertile women undergoing IVF. Contact with authors indicated that studies reporting on infertile women not undergoing IVF were not excluded rather this was the data that was available at the time. Historically IVF was used to treat women with TFI (Wang & Sauer, 2006). More recently, and especially after the advent of ICSI (intracytoplasmic sperm injection), IVF has been used in male factor infertility as well (Palermo, Joris, Devroe & Van Steirteghem, 1992; Sullivan et al., 2013; Wang & Sauer, 2006). It is possible that IVF samples could be over represented by certain types of diagnoses namely, TFI, male factor and unexplained infertility (Wang & Sauer, 2006). As such the IVF sample is not representative of the broader infertile population. Therefore generalizations to infertile women not undergoing IVF cannot be made.

There were other studies not included in the previously mentioned reviews that also reported an association between BV and adverse reproductive outcomes. Such outcomes included: miscarriage, preterm birth, premature rupture of the membranes and post-partum endometritis (Krohn, et al., 1995; Koumans & Kendrick 2001). Endometritis is an inflammation of the lining of the uterus due to an infection that is likely a precursor for adverse pregnancy outcomes like miscarriage, and preterm labour due to chorioamnionitis, an infection of the foetal membranes (Hay, 2004). In a study on adverse pregnancy outcomes and enzyme-producing microorganisms, BV was found to be associated with increased risk of preterm birth (RR 3.3, 95% CI 1.2 to 9.1, $p = 0.02$) and premature rupture of membranes (RR 3.8, 95% CI 1.6 to 9.0, $p = 0.002$) (McGregor, et al., 1994). In an examination of BV and recurrent pregnancy loss, BV was found to be twice as common in women who had had at least one late miscarriage (27/130; 21%) as in women who had had only first trimester pregnancy losses (31/370; 8%) ($P < 0.001$) (Llahi-Camp, et al., 1996).

The epidemiological and molecular level evidence summarized thus far lends support to the different pathways in Figure 3.5.2, with more definitive evidence available for the preterm pathway ('Pathway 3') via which fewer live births occur. However, evidence for the

other two pathways is more equivocal with some reports of associations between BV and STIs, endogenous infections and PID. Given the lack of RCTs and molecular level evidence to substantiate the exact mechanism of action of BV and the methodological weaknesses in extant research a meta-analysis of available studies would help provide more concrete evidence until such time as there is more substantial evidence. Although, van Oostrum and colleagues (2013) conducted such a study, and an update from 2013 to present might have been enough, their review examined effects in samples of women undergoing IVF only and some studies conducted prior to the review were not included. A new review is therefore, necessary to include all evidence.

Rational, Aim and Objectives

The biological plausibility of the effect of BV on reproductive process coupled with the association with adverse reproductive outcomes like preterm labour and TFI noted in the literature and the results of the survey of physicians [BV endorsed as a potential risk factor by 44.4% of responders] (Chapter 2, pp. 25), highlight the need to investigate whether BV should be included as a risk factor in the adapted FertiSTAT. BV has been noted as one of the long term consequences of FGM/C by the WHO (WHO, 2017, Female genital mutilation: Fact sheet), and a significantly higher odds of having BV was reported in women who had undergone Type II FGM compared with uncut women in Gambia (Morison, et al., 2001). This is especially relevant to regions where the prevalence of FGM/C is very high e.g. Sudan (88%; UNFPA-UNICEF, 2014). The WHO also noted BV as one of the conditions that increase an individual's risk of contracting HIV (WHO, HIV/AIDS: Fact Sheet). It is therefore important to investigate the nature and magnitude of the impact of BV on female fertility, regardless of whether it is an independent risk factor for infertility or impacts via other known risks.

The aim of the current systematic review was to determine whether BV should be included as a risk factor in the adapted FertiSTAT. To achieve this aim the present study sought to uncover evidence to determine whether BV has a negative impact on female fertility, the scale of this impact and whether the effect was on ability to become pregnant or have a live birth. The objective of the review was to examine whether BV was associated with fertility problems in women, and at what point in the reproductive process BV might exert its impact. The population of interest for the review was women, the exposure was BV and the outcome of interest was fertility problems.

Materials and Methods

Search Strategy

The search terms included words related to BV, for a complete list of MeSH terms see Appendix N. Studies were excluded if the acronym BV indicated something other than bacterial vaginosis, or only a specific species of bacteria.

Data Extraction and Quality Assessment

The data extraction form (Appendix H) was adapted to include information relevant to BV. The data-extraction form was adapted to include method used for the diagnosis of BV in included studies. The NOS form was adapted to reflect quality criteria for the assessment of BV and additional confounders. BV was adequately assessed if there was laboratory testing using the Nugent test during clinical examination or from hospital/medical records. The confounder that was more important than others was comorbid STIs.

Data Synthesis and Analysis

Meta-analyses were computed for the outcome found in the studies. Since these were all case-control studies data were calculated as previously described (pp. 65)

Subgroup analyses were planned to compare studies reporting on different types of infertility and studies using different outcomes. Since STIs might be an important aspect of the pathway (Figure 3.5.2), a subgroup analysis of women with STIs and those without was planned to enable conclusions to be drawn about the exact pathway.

Results

Study Selection

Figure 3.5.3 shows the PRISMA flowchart for number, reason and stage of exclusion of articles. A total of 184 records were identified (after duplicates removed) and most of those studies (123 of 184, 66.8%) were excluded because they did not measure fertility problems, no association between BV and fertility problems was reported or the association was reported following ART only. Of the 15 full text articles assessed for inclusion, eleven met inclusion criteria.

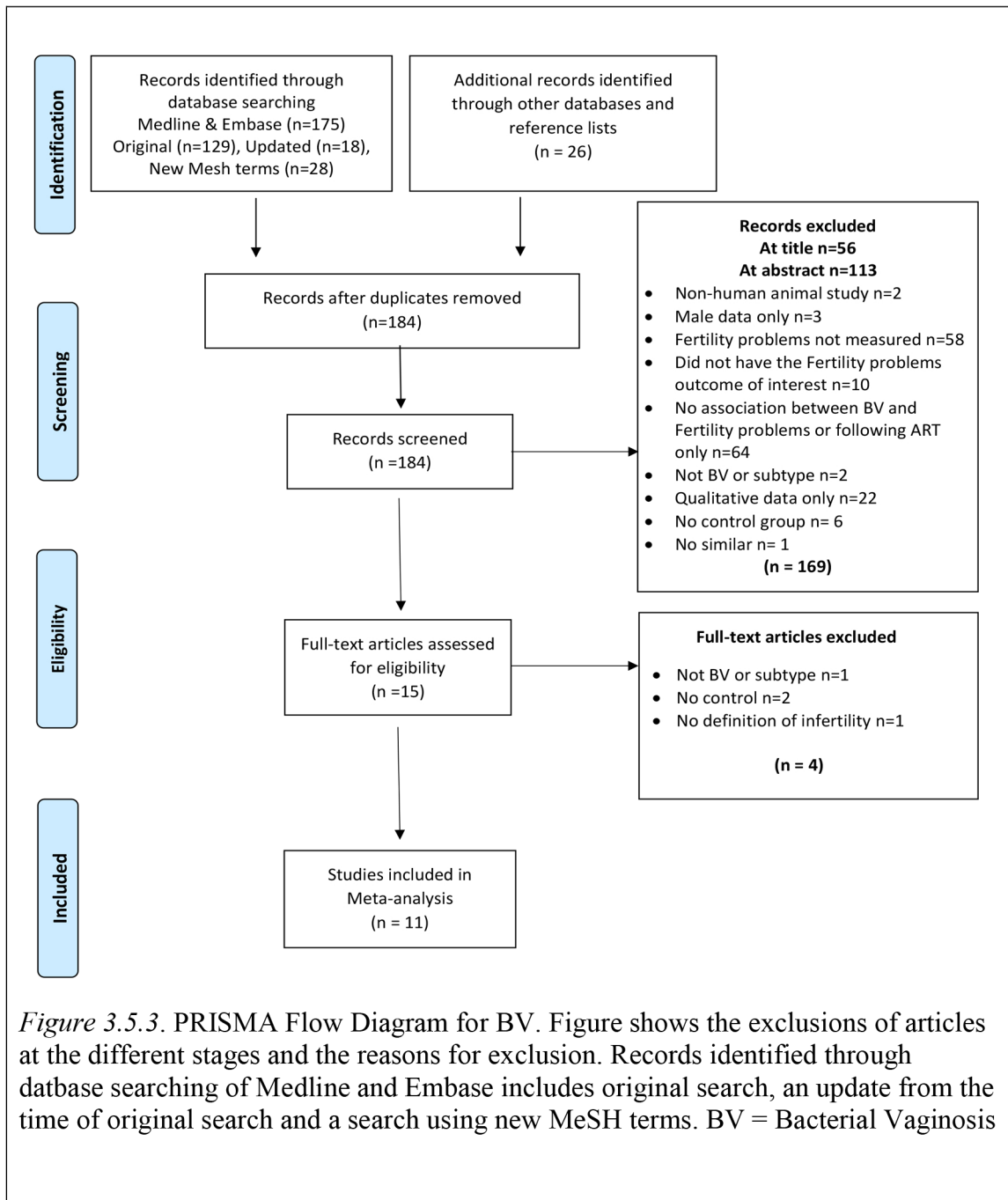


Figure 3.5.3. PRISMA Flow Diagram for BV. Figure shows the exclusions of articles at the different stages and the reasons for exclusion. Records identified through database searching of Medline and Embase includes original search, an update from the time of original search and a search using new MeSH terms. BV = Bacterial Vaginosis

Characteristics and Design of Included Studies

Due to a paucity of randomized controlled studies (RCTs) and cohort studies, only case-control and cross-sectional studies examining the percentage of BV in infertile women compared with fertile controls were available and included in the current review. Infertility was defined as inability to become pregnant in the majority (10 of 11) of included studies and inability to have a child in only one study, therefore, an examination of the impact of BV on

ability to have live births was not possible. Table 3.5.3 shows selected sample characteristics of the included studies. Almost half of the studies were conducted in Africa (5 of 11, 45.5%). Nine reported mean, median or range of age at time of study which was between 20 and 40, and two studies did not report on participant age. Table 3.5.4 shows methodological characteristics of included studies. Ten studies were case-control design and one was cross-sectional. Recruitment and biological sample collection (i.e., vaginal swabs) were carried out in hospitals or clinics in all 11 studies. BV was confirmed using Amsel clinical criteria in only one study, laboratory-based testing in 10 of the 11 studies, eight of those by means of gram staining using Nugent's scoring system, one using bacterial culture and one using culture or microscopy.

The primary outcome reported in the included studies was the diagnosis of BV (exposure to BV) in infertile (cases) and fertile (controls) women as noted (Chapter 3 Methods, pp. 65) the raw data were used to calculate the number of infertile women in the BV and No-BV groups. The definition of infertility varied in the included studies: four studies reported one-year duration of inability to become pregnant (of those, three were primary infertility and one was secondary infertility), two studies reported two years of inability to become pregnant, one study reported 36 months of inability to become pregnant (primary and secondary), two studies reported on TFI, one study reported idiopathic infertility and one study reported female factor infertility. The control groups also differed; three studies included pregnant controls, three studies included women who were reported to be fertile, two studies included women who had recently delivered (within 6 to 18 months) and two studies included women attending family planning clinic.

Table 3.5.3.

Sample Characteristics Reported in the Eleven Included Studies

Study	Location	Sample (n)	N			Age ^a Women	
			Infertile ^b	Fertile (control)		Infertile	Fertile
Case-control studies							
Aboul Enien, 2005	Egypt	60 women	40	20	Mean (SD)	NR	NR
Adamson, 2011	India	897 women	113	784	Mean (SD)	24.0 (3.4)	26.1 (3.0)
Almanza, 2011	Cuba	189 women	89	100	Mean	30.4	24.3
Dhont, 2010	Rwanda	571 women	307	264	Median (IQR)	30 (27–35)	27 (24–31)
Dhont, 2011	Rwanda	396 women	177	219	Median (IQR)	32 (28-37)	28 (25-32)
Durugbo, 2015	Nigeria	356 women	178	178	Mean (SD)	28 (5)	NR
					<20	0	6 (3.4)
					20-24	20 (11.2)	20 (11.2)
					25-29	77 (43.3)	66 (37.1)
					30-35	60 (33.7)	60 (33.7)
					>35	21 (11.8)	26 (14.6)
Kildea, 2000	Australia (Indigenous Women)	342 women	241	101	Mean (CI)	30.4 (95% CI, 29.7-31.1)	
Mania-Pramanik, 2009	India	214 women	112	102	Mean (SD)	In BV+ women 27.7 (5.2)	
Morgan, 1997	UK	1578 women	199	1379		NR	NR
Salah, 2013	Egypt	1256 women	874	382	Mean (SD)	27.1 (2.2)	25.8 (3.1)
Tomusiak, 2013	Poland	161 women	101	60	Range	20-40	

Note. ^a Age for women at the beginning of the study; ^b Unable to become pregnant after 1 or 2 years of unprotected intercourse, a specific diagnosis e.g. idiopathic, female factor; NR = not reported; SD = Standard deviation; IQR = inter-quartile range

Table 3.5.4.

Characteristics of the Design of the Eleven Included Studies

Study	Study design	Recruitment and data collection	Study period	BV self-report or lab test	Fertility Problems outcome measure (duration)	Control
About Enien, 2005	Case-control	Hospital based		Gram staining for the presence of BV using Nugent's scoring system	Diagnosed idiopathic infertility	Fertile women
Adamson, 2011	Case-control	Hospital based	2005-2006	Gram staining for the presence of BV using Nugent's scoring system	Primary infertility: married (or partnered) for more than two years, sexually active, not using modern contraception, and without children	Sexually active, not using modern contraception fertile women (not explicitly stated that they have a child, but only that they are fertile)
Almanza, 2011	Case-control	Hospital based	2009	Bacteriological culture techniques	Diagnosed tubal obstruction	Currently pregnant women about to deliver
Dhont, 2010	Case-control	Hospital based	2007-2009	Gram staining for the presence of BV using Nugent's scoring system and Amsel criteria	Infertility: having regular unprotected intercourse for 1 year or more without conception with at least one regular partner, and included both primary and secondary infertility. TFI subcategory	Non-pregnant women recently delivered (within past 6 to 18 months)
Dhont, 2011	Case-control	Hospital based	2007-2009	Gram staining for the presence of BV using Nugent's scoring system and Amsel criteria	Secondary infertility: having regular unprotected intercourse for one year or more with at least one regular partner without conception in women who conceived at least once before	Non-pregnant women recently delivered (between 6 and 18 months ago)
Durugbo, 2015	Case-control	Hospital based	2014	Visual assessment of discharge, then pH test, then 'whiff test' then microscopic examination ('fourth Amsel criteria')	TFI previously diagnosed by hysterosalpingography	Fertile women attending the family planning clinic
Kildea, 2000	Cross-sectional	Medical records	1996	Culture or microscopy	Primary infertility: never given birth to a live child despite 36 months of unprotected sexual intercourse. Secondary infertility: given birth to one or more live children in the past but now unable to become pregnant after 36 months of unprotected intercourse	Women who had been able to conceive within 36 months of unprotected intercourse
Mania-Pramanik, 2009	Case-control	Hospital based	NR	Gram staining for the presence of BV using Nugent's scoring system	Women who did not conceive within two years of marriage but were trying to conceive	Currently pregnant antenatal cases (first trimester, 2-3 months)
Morgan, 1997	Case-control	Clinic based		Gram staining for the presence of BV using Nugent's scoring system	Women attending at a specialist infertility clinic (trying to conceive for at least one year)	Currently pregnant (antenatal clinic)
Salah, 2013	Case-control	Hospital based	2009-2011	Gram staining for the presence of BV using Spiegel's criteria	Women diagnosed with female factor infertility	Attending family planning
Tomusiak, 2013	Case-control	Hospital/clinic based	NR	Gram staining for the presence of BV confirmed based on pH, Nugent score and quantitative culture results	Women in the infertile group had been treated for infertility for at least one year. Anatomical, hormonal abnormalities, endometriosis and abnormal sperm parameters ruled out	Women who had no history of fertility problems and at least one child

Note. BV = Bacterial vaginosis; TFI = tubal factor infertility; NR = not reported

Study Quality, Fertility Problems Outcome Measure and Bias

Table 3.5.5 shows the results of quality assessment (see table footnote for criteria). Infertility was adequately assessed in all the studies, as pre-specified in the quality assessment form (see Appendix H) but whether it was representative of the population could only be determined in six of the 11 included studies, see Table 3.5.4. The controls were adequately assessed in 10 of the 11 studies, but the adequacy of selection (selected from the same population) was reported in only five of the studies. Adequate assessment of confounders in the infertile/fertile groups was reported in six of the 11 the studies, but only three studies used the same method for both groups. Confounders were included in the analysis in six of the 11 reviewed studies, but only two (Durugbo, 2015; Kildea, 2000) included STIs. In addition to Durugbo (2015) and Kildea (2000), six other studies reported on ‘STIs’ but did not include STIs in the analysis. BV was adequately measured in eight of the included studies, as indicated by gram stain evaluated by Nugent’s criteria, not bacterial culture or clinical criteria. Overall the majority of studies (10 of 11) had high or average quality as per quality assessment. Follow-up criteria were not applicable to the included studies because they were case-control and cross-sectional, therefore there was no follow-up. Heterogeneity was significant and publication bias was explored using funnel plots, Eggers test, trim and fill procedures as well as subgroup analysis. Although a subgroup analysis was planned for the outcome ‘childlessness’, because only one study reported that outcome it could not be computed, instead the study was removed in a sensitivity analysis.

Percentages reported in Table 3.5.6 indicated that there were more infertile women in the BV group than in the No-BV group regardless of type of infertility. Additionally, the highest percentage of infertility was reported in the BV group in the exclusively TFI studies subgroup, see Table 3.5.5.

Table 3.5.5.

Quality Ratings for the Eleven Included Studies on the Basis of an Adapted Newcastle-Ottawa Quality Assessment Scale

Study	Quality Criterion						Overall rating ^g
	Adequacy of infertility (exposed) measure ^a Max 2 points	Adequacy of control (non-exposed), definition and selection ^b Max 2 points	Comparability of control ^c Max 2 points	Confounders adequately assessed Max 2 points ^d	Adequacy of outcome BV measure ^e Max 1 point	Loss to follow-up ^f Max 1 point	
Aboul Enien, 2005	2	1	0	0	1	NA	Average
Adamson, 2011	1	1	1	2	1	NA	Average
Almanza, 2011	1	1	1	1	1	NA	Average
Dhont, 2010	1	2	1	2	1	NA	High
Dhont, 2011	1	2	1	1	1	NA	Average
Durugbo, 2015	2	1	2	1	0	NA	Average
Kildea, 2000	2	2	2	2	0	NA	High
Mania-Pramanik,2009	1	2	0	0	1	NA	Average
Morgan, 1997	0	2	0	0	1	NA	Low
Salah, 2013	2	1	0	0	1	NA	Average
Tomusiak, 2013	2	1	0	0	1	NA	Average

Note. NA= not applicable; ^a Infertility was adequately assessed when independent validation of (e.g. laboratory testing and/or hospital/medical records) and it was representative of the cohort i.e. drawn from the same population (up to 2 points); ^b Controls were adequately assessed when selection was comparable to cases, and infertility was excluded properly in the control population (up to 2 points); ^c Comparability of controls was achieved if exposed/non-exposed were matched or adjustment during analysis conducted. One point for *STIs* and one point for any other confounder (up to 2 points); ^d Confounders were adequately assessed if they were obtained from records or a blind interview, and one point was given if the same method was used for both groups (up to 2 points); ^e Fertility problems outcome was adequately assessed if independent or blind assessment was stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.) (up to 1 point); ^f Point given if same rate for both groups and <20% loss to follow up reported; ^g The overall quality rating was low (0 to 3 points), average (4 to 6 points), or high (7 to 10 points).

Table 3.5.6.

Number and Percentage of Infertile Women in BV and No-BV Groups in the Included Studies (k=11)

Studies included	Number of women (%)	
	BV	No-BV
All studies k=11	846 of 1421 (59.5)	1443 of 4597 (31.4)
Exclusively TFI (subgroup) k=2	114 of 159 (71.7)	153 of 386 (39.6)
Not only TFI (subgroup) k=9	732 of 1262 (58.0)	1290 of 4211 (30.6)

Note. BV = bacterial vaginosis; TFI = tubal factor infertility

Results of Meta-analyses

The first analysis compared 11 studies with calculated data representing the proportion of infertile women in the BV and No-BV (control) groups, see Figure 3.5.4. This meta-analysis showed a significant pooled effect size (OR 2.81, 95% CI 1.85 to 4.27) and significant heterogeneity ($I^2 = 83%$, $p < 0.00001$). The results indicated that being in the BV group was associated with higher odds of being infertile (more likely to have fertility problems) than the No-BV control group.

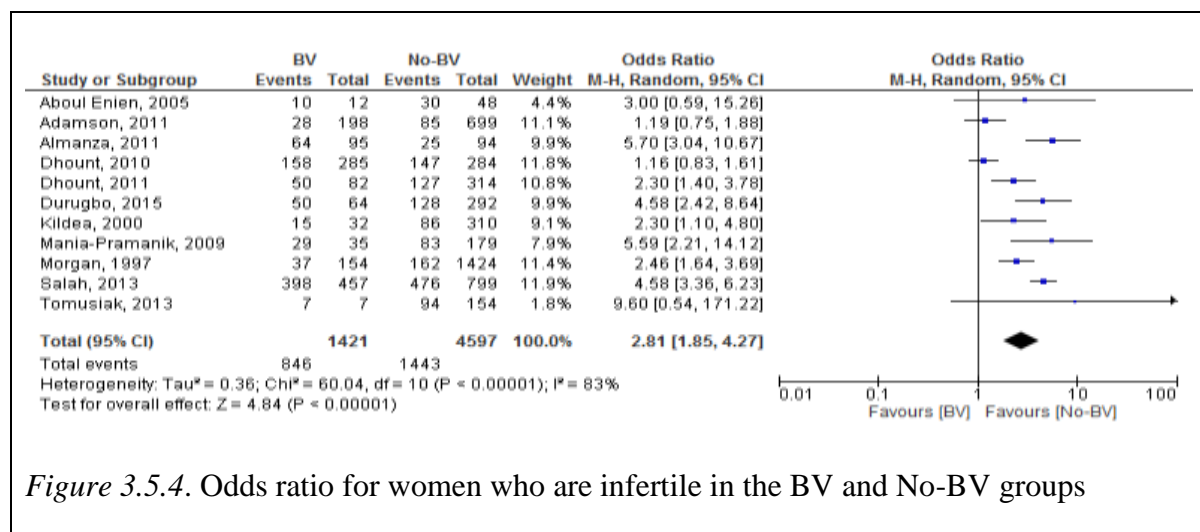


Figure 3.5.4. Odds ratio for women who are infertile in the BV and No-BV groups

Figure 3.5.5 shows the forest plot and meta-analysis result for the sensitivity analysis conducted by removing the one study reporting ‘inability to have a child’, and pooling the results of the 10 studies reporting ‘inability to become pregnant’. The meta-analysis showed a

significant pooled effect size (OR 3.12, 95% CI 2.03 to 4.79), but heterogeneity remained significant ($I^2 = 82\%$, $p < 0.00001$), see Figure 3.5.5. The results indicated that although both analyses were significant, the odds of being infertile in the BV group were higher if only women who were unable to achieve a pregnancy were included than if women who were unable to have a child were also included. Whether the difference between these two analyses was significant was not determined.

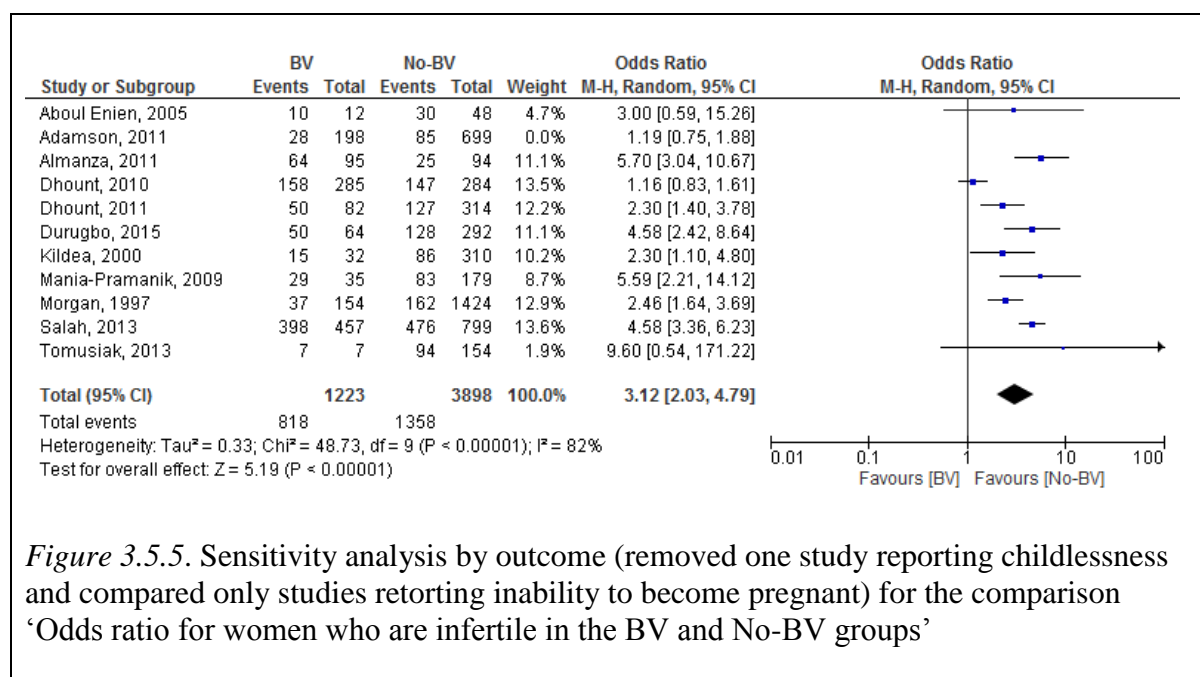
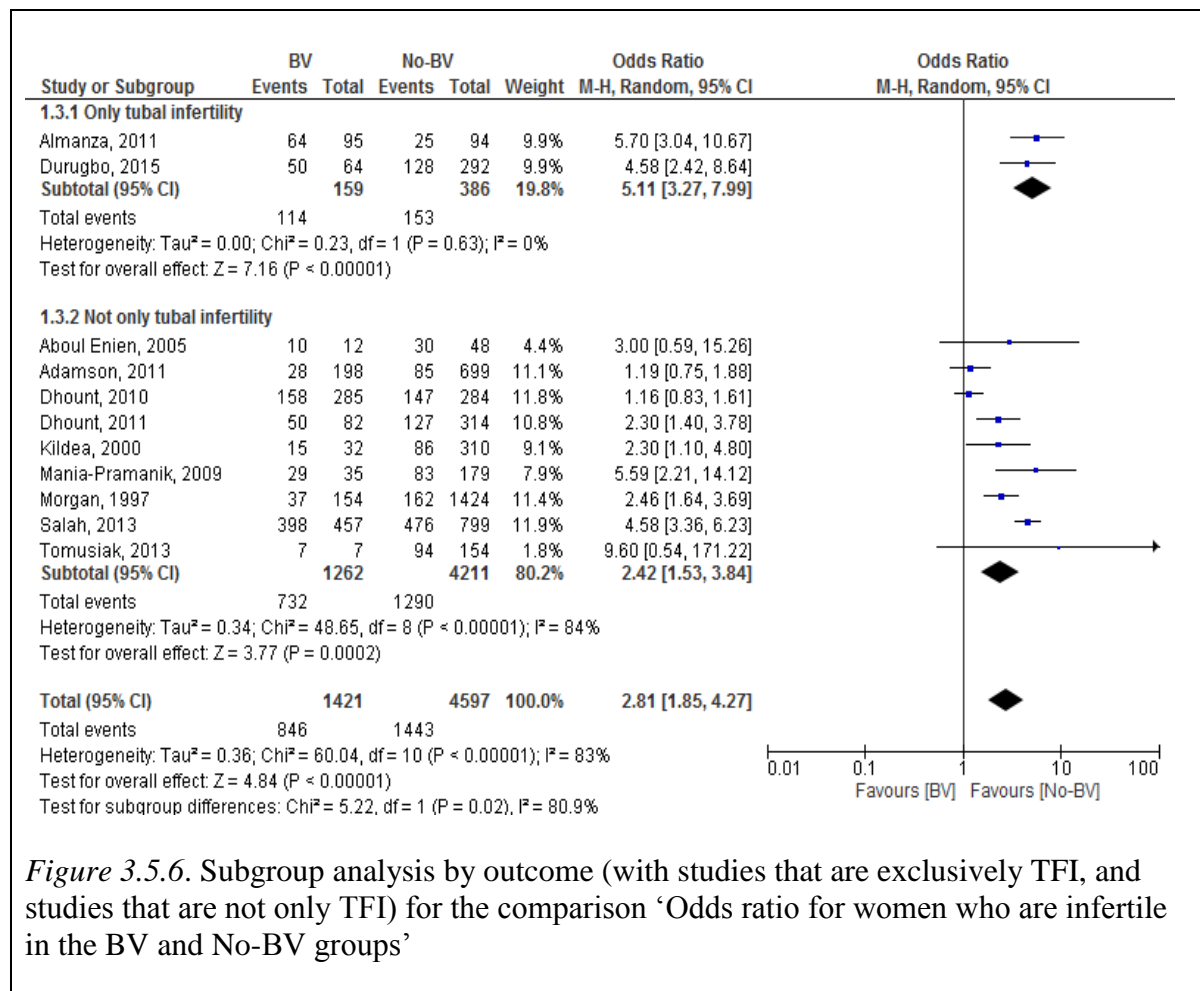


Figure 3.5.6 shows the subgroup analysis comparing the probability of being infertile in the BV and No-BV (control) groups in studies with ‘only TFI’ diagnoses compared with studies that were ‘not only TFI’ (multiple types of infertility). The subgroup that included the two studies reporting ‘only TFI’ showed a significant pooled effect size (OR 5.11, 95% CI 3.27 to 7.99), and non-significant heterogeneity ($I^2 = 0\%$, $p = 0.63$). The subgroup that included the nine studies reporting ‘not only TFI’ showed a significant pooled effect size (OR 2.42, 95% CI 1.53 to 3.84), and significant heterogeneity ($I^2 = 84\%$, $p < 0.00001$). The test for subgroup difference was statistically significant ($P=0.02$), indicating that the odds of an association between BV and ‘only TFI’ was significantly more than the odds of an association between BV and ‘not only TFI’. The results indicated that when only women

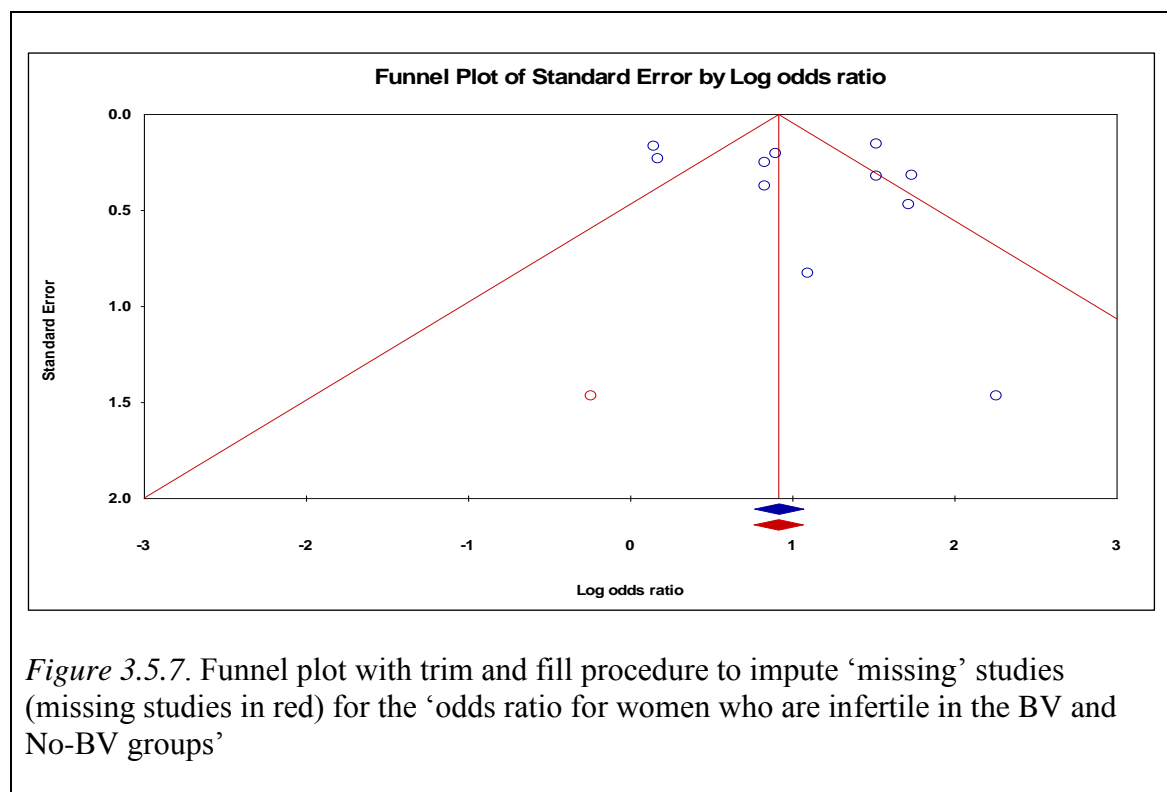
diagnosed with TFI were considered the odds of being infertile were higher in the women with BV than those without, as compared to lower odds if the infertile women had multiple types of infertility (not only TFI).



Publication bias assessment.

Publication bias was assessed using funnel plots, Eggers test and trim and fill procedures for the analysis ‘Odds ratio for women who are infertile in the BV and No-BV groups’. Egger’s test performed for the meta-analysis was not significant at $P < 0.05$, indicating the lack of publication bias. Trim and fill was used to estimate the number of ‘missing’ studies and if there were any changes to the magnitude of the pooled effect size if ‘missing’ studies were included. Figure 3.5.7 shows the procedure revealed one ‘missing’ study and the pooled effect size changed from (OR 2.81, 95% CI 1.85 to 4.27) to (OR 2.75,

95% CI 1.82 to 4.15), indicating that inclusion of the one ‘missing’ study would have reduced the difference between the BV and No-BV (control) groups but the BV group would still have significantly higher odds of infertility than the No-BV group.



STIs and Sexual History Reported in the Included Studies

Data were not available to enable a subgroup analysis of women with STIs and those without. Only a summary of percentages of women with STIs in the BV and No-BV groups was possible. Of the 11 studies included in the current meta-analysis, eight reported on STIs and four on sexual history, see Table 3.5.7. More STIs were found in the infertile women in all eight studies, except for more chlamydia found in the fertile group in one study (Tomusiak, 2013). Seven studies reported on the percentage of STIs in the infertile and fertile groups regardless of exposure to BV, see Table 3.5.7. In two of the included studies an association between BV and STIs was reported (Durugbo, 2015; Mania-Pramanik, 2009). In the first study, a history of STIs was significantly associated with BV (Durugbo, 2015). The

infertile group in this study included only women with a diagnosis of TFI. Of the 50 infertile women who had BV, 38 (74%) women had a history of STIs and of the 14 fertile controls that had BV, 11 (79%) women had a history of STIs. A history of STIs was more commonly found in the women with BV in both the infertile and fertile controls than in women without BV, see Table 3.5.7. In the second study, of the 29 infertile women who had BV, 5 (17.2%) women had comorbid STIs (Chlamydia and HPV) but none of the six pregnant controls who had BV had comorbid STIs (Mania-Pramanik, 2009). However, the significance of the differences between the infertile groups and the controls was not reported.

Table 3.5.7.

Percentage of Women with Comorbid STIs or a History of STIs in Infertile Versus Fertile Women in Eight of the Eleven Included Studies (k=8)

Study	Type of infection	Percentage of STIs			
		Infertile (%)		Fertile (control) (%)	
Adamson, 2011	HSV	22/113 (19.5)		81/784 (10.3)	
Almanza, 2011	Chlamydia	41/89 (46)		2/100 (2)	
	Mycoplasma hominis	15/89 (16.9)		10/100 (10)	
	Ureaplasma urealyticum	38/89 (42.7)		2/100 (2)	
Dhont, 2010	HIV	98/312 (32)		39/283 (14)	
	HSV	180/312 (59)		115/283 (41)	
Dhont, 2011	Chlamydia	57/312 (19)		44/283 (16)	
	HIV	74/177 (42)		35/219 (16)	
	HSV	121/177 (70)		99/219 (45)	
Kildea, 2000	Chlamydia	31/177 (18)		33/219 (15)	
	Chlamydia	36/101 (36)		68/241 (28)	
	Gonorrhoeae	42/101 (42)		51/241 (21)	
Tomusiak, 2013	Trichomonas vaginalis	64/101 (63)		95/241 (39)	
	Chlamydia	0/101 (0)		2/60 (3)	
	Mycoplasma hominis	4/101 (4)		0/60 (0)	
Durugbo, 2015	Ureaplasma urealyticum	9/101 (9)		5/60 (8)	
	History of STIs	64/178 (36)		35/178 (19.7)	
		Infertile/BV	Infertile/no-BV	Fertile/BV	Fertile/no-BV
Mania-Pramanik,2009	Chlamydia and HPV	38/50 (74)	26/128 (20.3)	11/14 (79)	24/164 (14.6)
		5/29 (17.2)	NR	0/6 (0)	NR

Note: HSV = herpes simplex virus; HIV = human immune deficiency virus; HPV = human papilloma virus; STIs = sexually transmitted infections; NR = not reported

Four studies also reported on sexual history. Infertility was significantly associated with younger age at sexual debut, risky sexual behaviour (e.g. unprotected sex) and increased number of lifetime sexual partners in three studies (Adamson, 2011; Dhount, 2010; Durugbo, 2015), and factors like unsafe abortion and pregnancy with a previous partner were associated with secondary infertility in the fourth study (Dhount, 2011). Additionally, having only one sexual partner was reported to be a protective factor against BV (Durugbo, 2015).

Discussion

Principal Findings

The results of the present set of meta-analyses suggest that BV may be a relevant factor associated with ability to become pregnant. One potential reason for the higher odds of infertility in women with BV proposed in the literature was increased susceptibility to other infections e.g. STIs (Wiesenfeld, Hillier, Krohn, Landers & Sweet, 2003) that lead to PID and consequently TFI (van Oostrum, et al., 2013; Morris, et al., 2001; Hay, 2004; Mastromariano, et al., 2014), 'Pathway 1 (a)' in Figure 3.5.2. The PID could also occur in the absence of STIs due to increased endogenous bacterial overgrowth typical of BV microflora (Korn, et al., 1995; Sweet, et al., 1987), 'Pathway 1 (b)' in Figure 3.5.2. Another potential pathway could be that the lack of lactobacilli characteristic of BV can lead to endometritis (Hillier et al., 1996) that could hinder implantation because of an immune response (Moore, et al., 2001; Spandorfer, et al., 2001; Hay, 2004), 'Pathway 2' in Figure 3.5.2. The difference between the subgroup analysis comparing women with 'only TFI' with those with 'not only TFI' was significant. This difference is clinically plausible and supported by evidence from the literature (Mastromariano et al., 2014; Morris, et al., 2001; Hay et al., 2012; van Oostrum, et al., (2013); Hay, 2004). The final arm of 'Pathway 1 (a)' that indicates tubal damage leads to infertility was supported by the finding of significantly higher odds of TFI compared to multiple types of infertility in women with BV than in women without BV.

However, the mechanism of how this blockage occurs remains unclear. The tubal blockage could be due to STIs leading to PID (Mastromariano et al., 2014), or it could be due to PID independent of STIs (Morris, et al., 2001; Hay et al., 2012), but the current results cannot support either mechanism. Additionally, the fact that the ‘not only TFI’ subgroup which included multiple types of infertility was also significant, suggested that either this sample included some women who had TFI, or that BV is also associated with other types of infertility e.g. anovulation, as reported in the literature (Morris, et al., 2001; Hay, 2004). This association could be examined by excluding all women with TFI from the ‘not only TFI’ subgroup and reassessing the meta-analysis. However, this was not possible in the current study because the type of infertility was not specified in all the include studies.

Other sub-group analyses could have helped provide evidence to the exact mechanism of action (e.g., types of infertility, comorbid STIs and PID) however, this was not possible from the current data. Although the second pathway in Figure 3.5.2 is biologically plausible, data from the current study could not be used to corroborate it. Evidence for the third pathway was not considered in the current review but is more concrete and therefore, requires less additional evidence.

It is important to note that two studies (Almanza, 2011; Dhount, 2010) reported percentage of BV in the infertile and fertile groups (72% and 52% respectively) that were higher than the highest estimate of BV reported in the literature, 50.9% in rural Uganda (Paxton, 1998). The higher percentage in Almanza (2011) can be explained by the fact that the bacterial culture method used to diagnose BV in this study is known to be less sensitive and can include many false positives (Money, 2005; Hillier, 1993). In the other study (Dhount, 2010), the fact that the study was conducted in Rwanda where the predominant race is black can be used to explain this high percentage, as black race has been found to be associated with higher percentages of BV (Hay, et al., 1994; Goldeberg, et al., 1996), and the

highest estimates of BV in the literature (50.9%) was reported in rural Uganda (Paxton, 1998).

An understanding of whether BV was associated with inability to achieve pregnancy or to have a child would have been gained from subgroup analysis based on a comparison of studies reporting inability to become pregnant with studies reporting inability to have a child. However, this was not possible because only one of the included studies reported inability to have a child (Adamson, 2011). Therefore, only a sensitivity analysis was conducted by removing the one study reporting childlessness. This analysis resulted in a larger pooled effect size, with higher odds of being infertile when only studies that considered the percentage of BV in women who were unable to become pregnant were included. However, making generalizations about the association of BV with childlessness are difficult at this time and would require more such studies.

In almost all the included studies the infertile women had more STIs (comorbid or history) than the fertile women. However, the association between STIs and BV was only reported in two studies (Durugbo, 2015; Mania-Pramanik, 2009). It can be inferred from the results of the first study (Durugbo, 2015) that a history of STIs was more commonly found in the women with BV in both the infertile and fertile controls than in women without BV. However, the results of the second study (Mania-Pramanik, 2009) indicate that BV was associated with STIs in the infertile women but not the fertile controls. The difference in the percentage of women with comorbid/history of STIs between these two studies could be related to the fact that in the first study (Durugbo, 2015) a history of STIs was measured while in the second study (Mania-Pramanik, 2009) a current STI was measured. Another reason for the difference could be the prevalence of STIs in the populations from which the studies were sampled. Durugbo (2015) was conducted in Nigeria and the prevalence of STIs in Africa is 7.2%, while Mania-Pramanik (2009) was conducted in India, and the prevalence in South-East Asia is 2.2% (WHO, 2012, Global incidence and prevalence of selected

curable sexually transmitted infections). Regardless of the reasons for the different percentages of STIs, these conflicting results make it difficult to draw conclusions to determine the involvement of STIs in 'Pathway 1 (b)' suggested in Figure 3.5.2, pp. 215. It can be inferred from the two studies that reported more cases of BV occurred with a history/comorbid STIs than without, regardless of fertility status, that STIs were also associated with BV. This data supports claims of increased susceptibility to, or comorbidities with STIs (van Oostrum, et al., 2013; Morris, et al., 2001; Hay, 2004; Mastromariano, et al., 2014); however, this requires more systematic evidence to be confirmed.

Overall it can be inferred from the results that exposure to BV was associated with infertility and that this association was stronger when only studies reporting on TFI were considered. The results indicated that women with BV were more likely to be infertile than women without BV. The results also indicated that the mechanism via which BV acts may be partially due to tubal damage, corroborating that the suggested mechanism of action may include the involvement of the fallopian tubes (van Oostrum, et al., 2013; Morris, et al., 2001; Hay, 2004). Whether the mechanism of tubal blockage was due to STIs and PID could not be established from current meta-analyses but data from the reviewed studies indicated higher percentage of STIs in infertile women, which is not surprising given that STIs are a well-established risk factor for infertility (NHS, April 2015; CDC, October 2016).

The criteria of 'biological plausibility', 'coherence' and 'consistency' were satisfied for BV due to the molecular level studies indicating the change in vaginal microflora, the consequential susceptibility to infection and immune response triggered by the abnormal microflora (see, Eckert et al., 2003; Hillier et al., 1996; Korn, et al., 1995; Moore et al., 2001; Spandorfer et al., 2001; Sweet, et al., 1987). These studies provide evidence for the first and second pathways in Figure 3.5.2. Molecular level evidence exists to support the first arm (weakening of membranes and/or labor cascade) of the third pathway in Figure 3.5.2 (Hillier,

et al., 1988; Heller et al., 2003; Goldenberg et al., 2000; Sebire, 2001) and epidemiological evidence for the rest of the pathway (preterm labor), see (Hay, 2004; Hay et al., 2012; Mastromarino et al., 2014; Morris et al., 2001).

There is systematic evidence that shows that although treatment of BV during pregnancy does not prevent preterm birth, in women with abnormal flora (intermediate flora and BV) treatment helps reduce the risk of preterm birth (McDonald et al., 2007), suggestive of a dose-response effect, thus satisfying the ‘biological gradient’ criteria. The evidence from these studies combined with the fifth criteria ‘strength’ of the relationship found in the current meta-analysis (more than double chance of being infertile in the BV group and a fivefold increase when the infertility was TFI only), should bolster the likelihood that there is a causal relationship between BV, infertility generally and TFI specifically. However, more evidence is necessary to identify whether the increased susceptibility is due to STIs or to endogenous infections that could affect treatment protocols in infertile patients with BV.

Justification for including BV in the FertiSTAT.

The current meta-analyses indicated that inclusion of BV in FertiSTAT as a new risk factor could potentially increase the predictive ability of the tool in LMIC. If the mechanism of action of BV was only via tubal blockage caused by STIs or PID, then it would not be an independent risk factor since STIs and PID are risk factors in the original tool and the inclusion of BV would not increase the predictive ability of the tool. However, the fact that significantly higher odds of being infertile in the BV versus No-BV group even when the type of infertility was not limited to TFI, indicated that there may be more than one mechanism via which BV operates. Had an analysis been performed that excluded all women with TFI it would have been possible to draw conclusions about the pathways that do not involve PID and the consequential tubal damage. However, as previously mentioned, this was not possible due to lack of data. Additionally, the involvement of post-pregnancy outcomes (e.g., preterm birth) were not examined since such outcomes were not used in the primary studies identified

in the current review. Therefore, the results of the current study do not allow confirmation of the second and third causal pathways which involved post implantation and preterm birth, see Figure 3.5.2.

Implications of Findings

Results of the current study indicated that there was sufficient evidence to determine that BV is associated with infertility generally and TFI specifically. Whether this effect is mediated or moderated by other factors such as STIs could not be determined from the current data, nevertheless, awareness of the risks associated with BV should be communicated to women.

The main implication of the results of this review is that women and health care providers should be made aware of potential risks to reproductive health that women who have untreated BV (including intermediate level microflora) face. The results of the review lend support to reports in the literature of an association between BV and TFI that can hinder a women's ability to become pregnant (van Oostrum, et al., 2013; Morris, et al., 2001; Hay, 2004). The repercussions of the potential damage to the fallopian tubes due to untreated BV and the potential increased susceptibility to STIs and/or PID for couples wanting to become pregnant are important because of its impact on childbearing. An understanding of whether the tubal damage results directly from the BV leading to PID or to intermediate infections like STIs that lead to PID needs to be examined as the treatment and management guidelines may vary depending on the mechanism of action.

With regard to BV specifically, the WHO report on pre-pregnancy care (see WHO, Meeting report, 2012), did not include information on the association between BV or about the management of BV before pregnancy or during pregnancy (WHO, Meeting report, 2012). However, the results of the current meta-analyses strengthen the evidence base required to include BV screening as an additional aspect of a comprehensive pre-pregnancy package. NHS guidelines for BV recommend that women should consult a GP if they notice

abnormal vaginal discharge, especially if pregnant (NHS, October 2015), however, in the UK, screening for BV is not part of pre-pregnancy care. UK guidelines for the management of BV indicate that the evidence for screening and treating BV during pregnancy is conflicting and therefore make no recommendations about screening (Hay, et al., 2012). With regards to treating women with BV, UK guidelines recommend that based on the evidence currently available treatment should be as usual for symptomatic pregnant women (Hay, et al., 2012). However, they note that there is insufficient evidence for the treatment of asymptomatic pregnant women, but that pregnant women at additional risk of preterm birth could benefit from treatment before 20 weeks' gestation (Hay, et al., 2012). This recommendation was based on a Cochrane review (McDonald, Brocklehurst & Gordon, 2007), but a recent update of that review revealed that the risk of preterm birth was not reduced with treatment for BV (Brocklehurst et al., 2013). The authors recommend that there is little value in screening or treating all pregnant women in preventing preterm birth, however, if screening criteria include women with abnormal flora (broader than BV) there was a significant reduction of preterm birth (Brocklehurst, 2013). All these recommendations are for preterm birth, whether there is value in screening women for BV before pregnancy to prevent STIs and PID to avoid complications like TFI and impaired implantation remains to be examined.

Strength and Limitations in Included Studies

The heterogeneity in study methodology, outcome measures and sample size in included studies could affect the comparability of these studies, and the generalizability of the results of this review. Heterogeneity in fertility problem outcomes (inability to become pregnant, being childless, TFI) and data collection methods (diagnosis of BV and infertility, subtypes of infertility), can affect the practical applicability of the results. Heterogeneity remained statistically significant in subgroups and sensitivity analyses indicating that overall issues of

methodological heterogeneity persisted, suggesting that uniformity in study methodology is required before pooled estimates are recalculated. The quality of each study independently does not appear to affect the overall results of the review since all of studies were of sound quality as determined by the Newcastle-Ottawa quality assessment scale. Bias relating to the primary studies included selection bias and information bias. In hospital and clinic based studies, the selection of participants based on hospital attendance can reduce the generalizability of the results. However, because the same sampling procedures were used for both cases (exposed) and controls (non-exposed), we can assume that selection bias may not be substantial. It can be assumed that since the selection of participants was from the same sample and information was gathered using the same method for both the exposed and non-exposed groups in all the studies, that selection and information bias may not affect results considerably. Bias due to confounder was a potential limitation of the studies included because matching the groups for confounders was reported in five of the included studies. The most important confounder 'comorbid STI' which is known to impact negatively on fertility was reported in eight of the eleven studied but included in the analysis of only two studies. There could have been an unequal distribution of other confounders in the case and control groups. However, the effect of confounders e.g. sexual history, marital status, age, that could have influenced the relationship between BV and fertility problems was taken into consideration via either matching groups for confounders or entering them into analysis in five studies.

Another limitation relating to the primary studies is the use of observational designs, as discussed in previous reviews. The fact that all of studies included in this review were case-control in nature, which are reasonably rigorous in identifying associations (Mann, 2003), limits the determination of a causal relationship between BV and infertility. As in the case of consanguinity, randomization for exposure to BV would not have been possible or ethical, but randomization might be possible for screening for BV. Alternatively, the most

rigorous design to compare exposed and non-exposed individuals would be cohort studies, followed by case-control and then cross-sectional (Mann, 2003).

Future research

Future research to disentangle the effect of BV on fertility problems requires, RCTs and prospective cohort studies to investigate the causal mechanisms that are involved. Additionally, molecular level studies need to consider the specific microflora changes typical of BV and the associated consequences such as increased susceptibility to STIs, to support the first part of ‘Pathway 1 (a)’ in Figure 3.5.2. Ideally, RCTs that examine risk of infertility in samples of women screened and treated versus unscreened for BV should be conducted. Such a study would assess the benefit of screening women for BV, STIs and PID and measuring outcomes like pregnancy, infertility generally and TFI specifically and other reproductive outcomes. Additionally, longitudinal prospective cohort studies should be conducted to follow women exposed (at risk) to BV and non-exposed (not at risk) women as well as women treated/untreated, with measurements at baseline and follow-up of reproductive outcomes such as STIs, PID, tubal blockage, pregnancy rate (clinical versus biochemical), pregnancy outcomes e.g. first and second trimester losses, preterm labour, preterm birth and premature rupture of membranes. Additionally, confounders such as sexual history, comorbid STIs and PID should be considered in study methodologies (e.g. included in statistical analysis). It will be important to determine which aspects of the reproductive process are affected to determine whether implantation is being impacted or if tubal blockage is occurring, and whether it was preceded with PID (with or without STIs). Future research should be directed at understanding the reasons for the higher odds of being infertile (TFI compared with multiple types of infertility) in women with BV, to definitively ascertain if it is related to blocked tubes. Studies sampling only women with TFI should be compared

with studies that exclude TFI. It is important to investigate BV during pregnancy to determine the nature of the relationship between BV and the different stages of pregnancy. This would help identify the exact biological mechanisms involved, which would in turn determine the differential management required. It is imperative that after more such studies are carried out that an update of the current meta-analyses be conducted.

Conclusion

Fertility problems have been reported as a negative consequence of BV in the literature but evidence to support this claim has been equivocal. Results of the current meta-analyses indicated that BV was associated with an inability to become pregnant, and this appeared to be related to tubal blockage. The results were not sufficient to rule-out an association between BV and non-TFI. Therefore, there appear to be several pathways through which BV can impact fertility and evidence from molecular level studies, and previously reviewed epidemiological studies lend support to the three pathways suggested in this review. In light of these results the inclusion of BV in the adapted FertiSTAT could potentially increase the predictive ability of the tool. It is important to note that this area of research should be re-examined when more research is accumulated.

Study 3.6: Systematic Review of Observational Studies Examining the Association of Repeated Dilatation and Curettage and Fertility Problems

Introduction

Repeated dilatation and curettage (D&C) was one of the risk factors endorsed by participants in the survey of international fertility doctors (Chapter 2, pp 25). The validity of this risk factor as a predictor of fertility problems was examined in the current systematic review using the methodology reported in the General Methods of Chapter 3 (pp. 58).

Description of D&C and reproductive health consequences

D&C is a gynaecological procedure performed to remove tissue from the uterus for various clinical indications (see below) (NHS Suffolk Public Health Team, 2013). The D&C procedure involves dilation of the cervix with an instrument or medication and the scraping of the inside of the uterus with a curette, a metal instrument, see Figure 3.6.1 and 3.6.2.

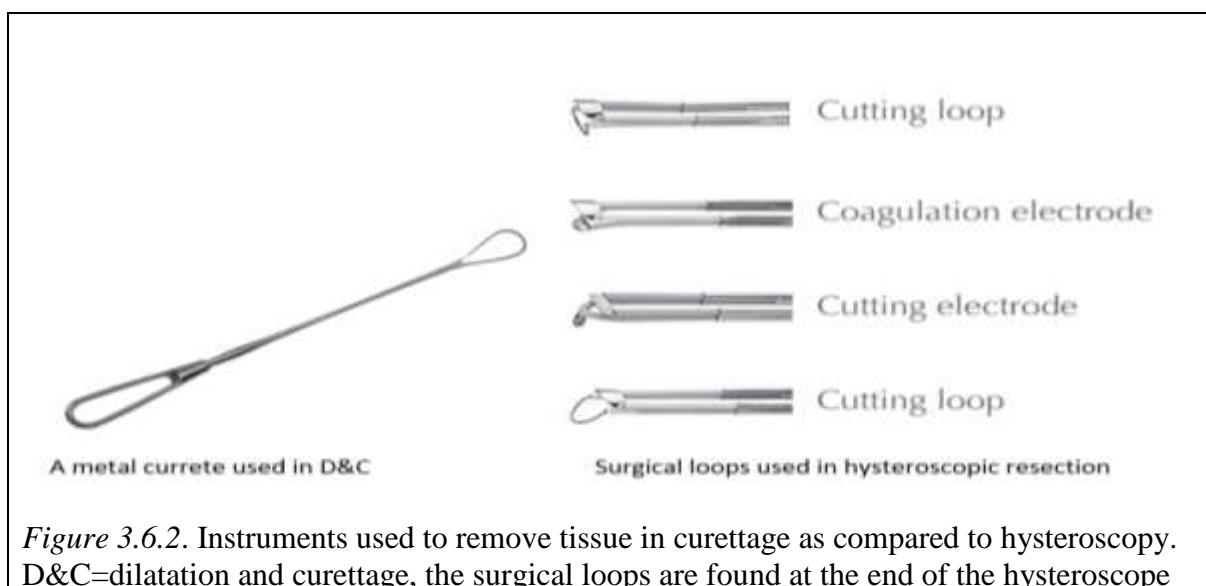
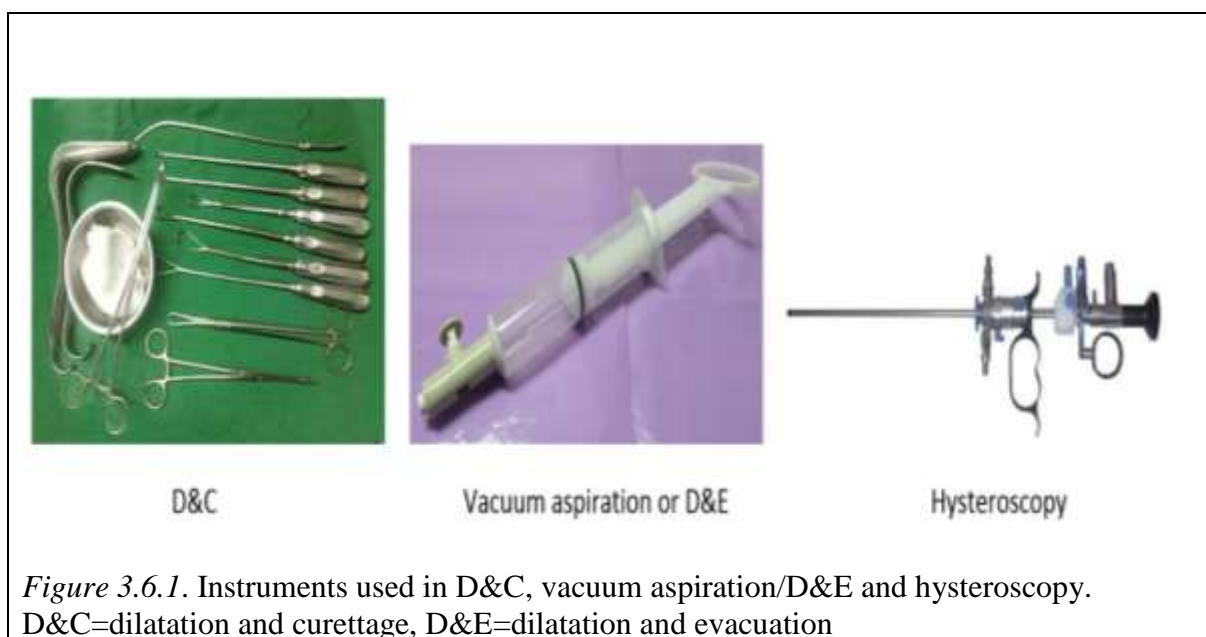
To understand the body of evidence some medical terminology used in the literature needs to be clarified. ‘Repeated D&C’ refers to having the procedure more than once over time (weeks, months, years), not twice on the same occasion. Abortion indicates induced abortion not miscarriage unless otherwise specified. An induced abortion is defined as intentional loss of intrauterine pregnancy through medical or surgical intervention (Zegers et al., 2017). Medical management is used to indicate non-surgical treatment with medicines such as misoprostol and prostaglandins. Retained products of conception (RPOC) refers to placental or foetal tissue that remains in the uterus after birth, miscarriage or abortion. Negative pregnancy outcomes refers to any outcome of pregnancy that does not lead to a healthy live birth including gestational problems like miscarriage, ectopic pregnancy and still

birth. Obstetric history is a medical term indicating all previous obstetric events, for example, pregnancy, miscarriage, abortion, live birth, post-partum infection and premature birth.

It is also important to consider these three factors when reviewing the literature: clinical indications for the procedure, type of procedure(s) and outcome after the procedure(s). First, the clinical indications for D&C include (but are not limited to) to: (1) treatment of abnormal uterine bleeding, (2) induce abortion, (3) ensure miscarriage is complete, (4) remove RPOC after miscarriage, abortion or birth, and (5) endometrial sampling necessary for diagnoses of diseases like cancer. There is also anthropological evidence that D&C was historically used to ‘cure’ infertility or to enhance a woman’s ability to become pregnant (Inhorn and Buss, 1993). It is important to consider the clinical indications because they could have different impact due to the difference in gynaecological and obstetric history, for example previous infections, or miscarriages, abortions or births could have led to biological alteration to the reproductive system.

Second, some of the procedures used in control groups compared to D&C include but are not limited to: (1) hysteroscopy or hysteroscopic resection, the insertion of a thin lighted tube (telescope) to examine the cervix and uterus and to remove tissue using a surgical loop at the end of the hysteroscope (2) vacuum aspiration, dilatation and evacuation (D&E), both procedures use suction to remove materials from the uterus (not a curette), (3) medical management with misoprostol or prostaglandins (medications that cause uterine contractions), and (4) expectant/conservative management (waiting). It is important to note that in some studies surgical procedures are grouped together. These surgical procedures are D&C, vacuum aspiration, D&E and hysteroscopy, and all involve a form of surgical intervention. Figure 3.6.1 shows the different equipment used in these surgical procedures and Figure 3.6.2 compares the metal instrument used to remove tissue. The procedures could have different impact for the following reasons: (a) all procedures other than medical and

expectant management that use dilatation have the potential to damage the cervix, (2) in medical and expectant management there is the risk of incomplete evacuation of products of conception, which could lead to complications such as bleeding, (3) the difference between D&C and all procedures using suction is that scraping of the uterus with a sharp instrument is done in D&C, (4) the difference between all procedures and hysteroscopic resection is that hysteroscopy allows for visualization of the procedure, while all other surgical interventions such as D&C are blind, see Figure 3.6.2.



Third, regarding outcomes, all outcomes reported are complications that occur after the management (surgical, medical or waiting) that are considered a deviation from the normal post-operative sequel. Some studies report on short-term consequences such as prolonged bleeding that occur immediately after the procedure and others report on long-term consequences such as intra uterine adhesions (IUAs) and pregnancy rate that occur sometime in the future not immediately after the procedure. Short and long-term outcome could also be linked, for example prolonged bleeding right after the procedure might be linked to developing IUAs. Since the literature is not extensive all available evidence was reviewed and conclusions about the impact of repeated D&C on fertility, inferred from an evaluation of the consolidation of all the available evidence. An examination of the literature would enable inferences to be made about whether: (a) it is the D&C or the clinical indications for its use that has negative reproductive consequences, (b) a single D&C can cause harm, (c) other types of surgical interventions such as vacuum aspiration are equally harmful, more so than medical treatment (misoprostol) or waiting, (d) short-term consequences can predict long-term outcomes and consequently the appropriate treatment of short-term problems can lead to better prognosis, (e) there are other confounding variables that moderate, mediate or completely explain the effect of D&C (e.g. post-operative care or experience of the professional conducting the D&C).

Negative reproductive outcomes after the procedure of D&C have been reported historically and in more recent literature, a summary of these findings is presented in Table 3.6.1. In older research (Pre 2000, see Table 3.6.1), the negative consequences reported after a single D&C included IUAs, secondary infertility and negative pregnancy outcomes (e.g. spontaneous abortion). In the same literature, repeated D&C was associated with negative pregnancy outcomes (e.g. ectopic pregnancy) and infertility (in cases where PID occurred after D&C). Specifically, in a review, Hogue and colleagues (1983) reported that the

evidence for the effect of multiple induced abortions whether using D&C only or D&C and Vacuum aspiration, on reproductive problems was inconclusive (Hogue, Cates & Tietze, 1983). The authors reported that some outcomes such as ectopic pregnancy were reported in some primary studies but not others, and that this could be due to the method used for the abortion but also whether the abortion was legal or not (Hogue, Cates & Tietze, 1983). It is important to note that the results in this review pertain to the exposure to ‘multiple abortions’ rather than the specific procedure performed (Hogue, Cates & Tietze, 1983).

Table 3.6.1.

Summary of Long-term Negative Reproductive Outcomes Reported as a Consequence of D&C in the Literature

Reproductive outcome	Long-term negative reproductive outcome	Primary study or review
Historical literature (up to 2000)		
Single D&C	Intrauterine adhesions (IUAs), Asherman’s syndrome (30.9% of women who had D&C after miscarriage)	Schenker & Margalioth, 1982; Schenker, 1996
	Secondary infertility (after spontaneous miscarriage as a complication of the intrauterine surgery)	Schenker & Margalioth, 1982; Schenker, 1996
	Recurrent miscarriages (after spontaneous miscarriage as a complication of the intrauterine surgery)	Schenker & Margalioth, 1982; Schenker, 1996
	Negative pregnancy outcomes* after D&C (e.g. higher rates of spontaneous abortion), incompetent cervix**, preterm labour, preterm rupture of membranes, early neonatal death, and ectopic pregnancy)	Madore, Hawes, Many & Hexter, 1981; Linn et al., 1983; Kalish, Chasen, Rosenzweig, Rashbaum & Chervenak, 2002
Repeated D&C	Negative pregnancy outcomes after repeated D&C (e.g. first trimester bleeding, abnormal presentations, placenta abruption, foetal distress, low birth weight, short gestation, and major malformations)	Linn, 1983
	Primigravida abortion was only associated with infertility in cases where infection was present and consequently PID occurred	Hogue et al., 1983 (review)
	D&C as compared to vacuum aspiration was associated with negative reproductive outcomes (ectopic pregnancy, mid-trimester spontaneous abortion and low birth weight)	Hogue, 1986 (review)
Current literature (2000-present)		
Single D&C	Significantly more IUAs were found after D&C compared with hysteroscopic resection*** (30% vs. 13%)	Hooker et al., 2016 (review)

Reproductive outcome	Long-term negative reproductive outcome	Primary study or review
	More postpartum haemorrhage in pregnancy following D&C (as compared to the literature)	Lohmann-Bigelow et al., 2007
Repeated D&C	Odds of developing IUAs after repeated (>1) D&C were greater than after one D&C (OR 2.05, 95% CI 1.35–3.12, P=0.0008)	Hooker et al., 2014 (review)

Note: D&C= dilatation and curettage, IUAs= intrauterine adhesions, PID=pelvic inflammatory disease, *Negative pregnancy outcomes are all the outcomes of a pregnancy that do not lead to a live birth (e.g. gestational problems, stillbirth) **incompetent cervix = cervical insufficiency i.e. weak cervical tissue contributes to premature birth. ***hysteroscopic resection is the removal of tissue from the uterus using a hysteroscope.

More current literature such as a Cochrane review of RCTs have shown that differences in short-term complications like blood loss of first trimester termination of pregnancy using D&C compared to vacuum aspiration were not statistically significant (Kulier, Cheng, Fekih, Hofmeyr & Campana, 2001). The authors reported that long-term outcomes (such as fertility) were not available in the 11 included studies (Kulier et al., 2001).

In a more recent Cochrane review of seven RCTs of expectant management (EXP) versus surgical treatment (vacuum aspiration or D&C) for miscarriage, the authors reported that women in the EXP group were significantly more likely to experience short-term consequences (require surgery after the initial treatment, prolonged bleeding and need for transfusion) (Nanda, Lopez, Grimes, Peloggia & Nanda, 2012). The two groups were not reported to differ significantly with regards to infection. Additionally, pooled effects for long-term outcomes such as future pregnancy or live births were not computed (Nanda et al., 2012). These Cochrane reviews were included to provide evidence for the short-term consequence of D&C and other procedures because the link between short and long-term outcomes has not been examined but may prove to be important.

In a systematic review, the odds of developing IUAs after repeated (>1) D&C were greater than after one D&C (OR 2.05, 95% CI 1.35–3.12, P=0.0008) (Hooker et al., 2014). Additionally, the effect of D&C on long-term reproductive outcomes like future pregnancy and live birth was summarized but pooled estimates were not reported in the review (Hooker

et al. 2014). The summary comprised five studies reporting on live birth and/or pregnancy rates after miscarriage in women who had undergone D&C as compared to women who had had other management (i.e., EXP or medical management with misoprostol [MED]). From the summary of these studies it was concluded that the future pregnancy or live birth rate after miscarriage in women treated with D&C as compared to EXP or MED management did not differ. However, an examination of these primary studies, proposed by Hooker et al. (2014) to be reporting on D&C, indicated that four were in fact studies using surgical interventions that involved suction not D&C (Blohm, et al., 1997; Graziosi et al., 2004; Smith et al., 2009; Tam et al., 2005). Only Ben-Baruch et al. (1991), reported on D&C and therefore was included in the current study.

In a systematic review examining the long-term outcomes after management of retained products of conception (RPOC), Hooker and colleagues (2016) reported significantly more IUAs were encountered after D&C compared with hysteroscopic resection (30% vs. 13%) (Hooker, Aydin, Brolmann & Huirne, 2016). It was also reported that women treated for RPOC (D&C compared to hysteroscopic resection) had a similar rate of pregnancy and live birth. Of the three studies reporting long-term consequences summarized in this review, one used D&E (ultrasound-guided evacuation) not D&C (Rein et al., 2011), one used D&C but in some cases they went back and did hysteroscopy so it is not possible to identify which outcomes are related to D&C (Cohen et al., 2001) and the third (Ben-Ami, 2014) was obtained from the original search (details in results section, pp 265).

The evidence presented thus far suggests the need for a systematic review and makes clear that the relationship between D&C and future reproductive outcomes is complicated by several factors. First, the clinical indication for the procedure differs within and between studies making the effect of D&C difficult to separate from that of the indication. Second, the number of times the procedure is performed could determine its impact on fertility outcomes.

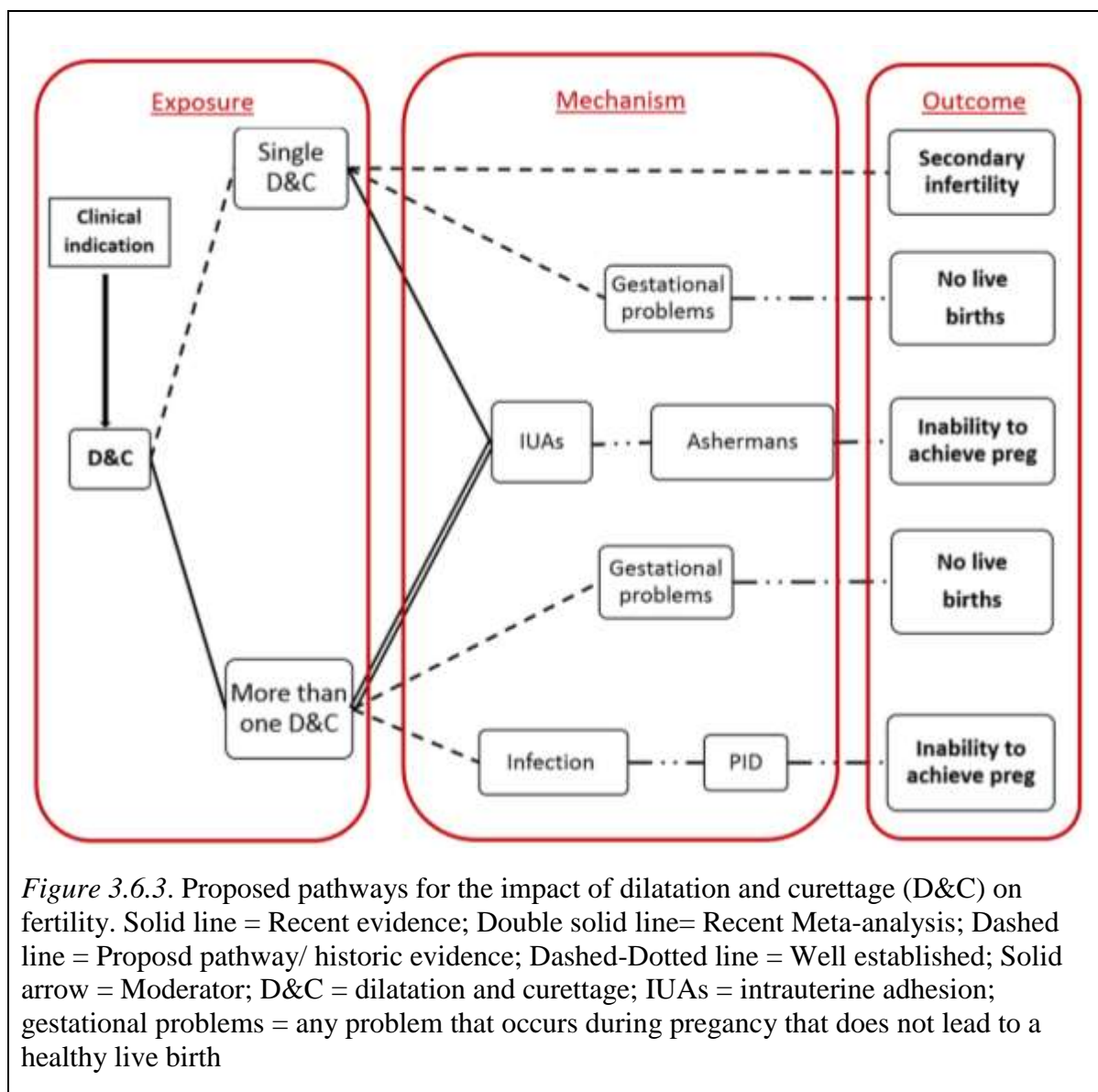
Finally, there is heterogeneity in control groups, outcomes and follow up periods (short and long-term) reported. The lack of compelling evidence for or against the impact of D&C on long-term reproductive outcomes (infertility, pregnancy and live birth rates), coupled with the heterogeneity in primary study methodologies supports the need to conduct the current systematic review.

Plausible Mechanisms to Explain why D&C Could be Associated with Fertility

Problems

All the evidence from the literature summarized thus far would suggest that D&C could impact fertility as a result of a single procedure or as a result of multiple procedures (more than one D&C). Figure 3.6.3 shows the proposed pathways and the level of evidence available for each. It can be seen from Figure 3.6.3 that IUAs (pathways 3 and 4) and gestational problems (pathways 2 and 5) are associated with single procedure and multiple procedures. A single procedure is also associated with secondary infertility (pathway 1), while multiple procedures are associated with infection and PID (pathway 6).

The biological plausibility of the effect of D&C on reproductive processes coupled with the association with adverse reproductive outcomes like increased IUAs noted in the literature, highlight the need to investigate whether D&C should be included as a risk factor in the adapted FertiSTAT.



Rational, Aim and Objectives

The aim of the current systematic review was to determine whether repeated D&C should be included as a risk factor in the adapted FertiSTAT. This was achieved by systematically reviewing the literature to determine whether repeated D&C was associated with fertility problems in women, and at what point in the reproductive process the impact occurs. The population of interest for the review was women, the exposure was to the procedure of D&C more than once and the outcome of interest was fertility problems.

Materials and Methods

Search Strategy

The search terms included words related to D&C, for a complete list of MeSH terms see Appendix O. The search was limited to humans due to the large number of animal studies. Studies were excluded if the acronym D&C referred to or meant something else.

Data Extraction and Quality Assessment

The data extraction form (Appendix H) was adapted to include information relevant to D&C. Specifically, data about ‘obstetric history’ (e.g. pregnancy, miscarriage, abortion, live birth, post-partum infection and premature birth). The NOS form was adapted to reflect quality criteria for the assessment of D&C and additional confounders. D&C was adequately assessed if there were medical/hospital records indicative of the procedure performed. The confounder that was more important than others was ‘obstetric history’.

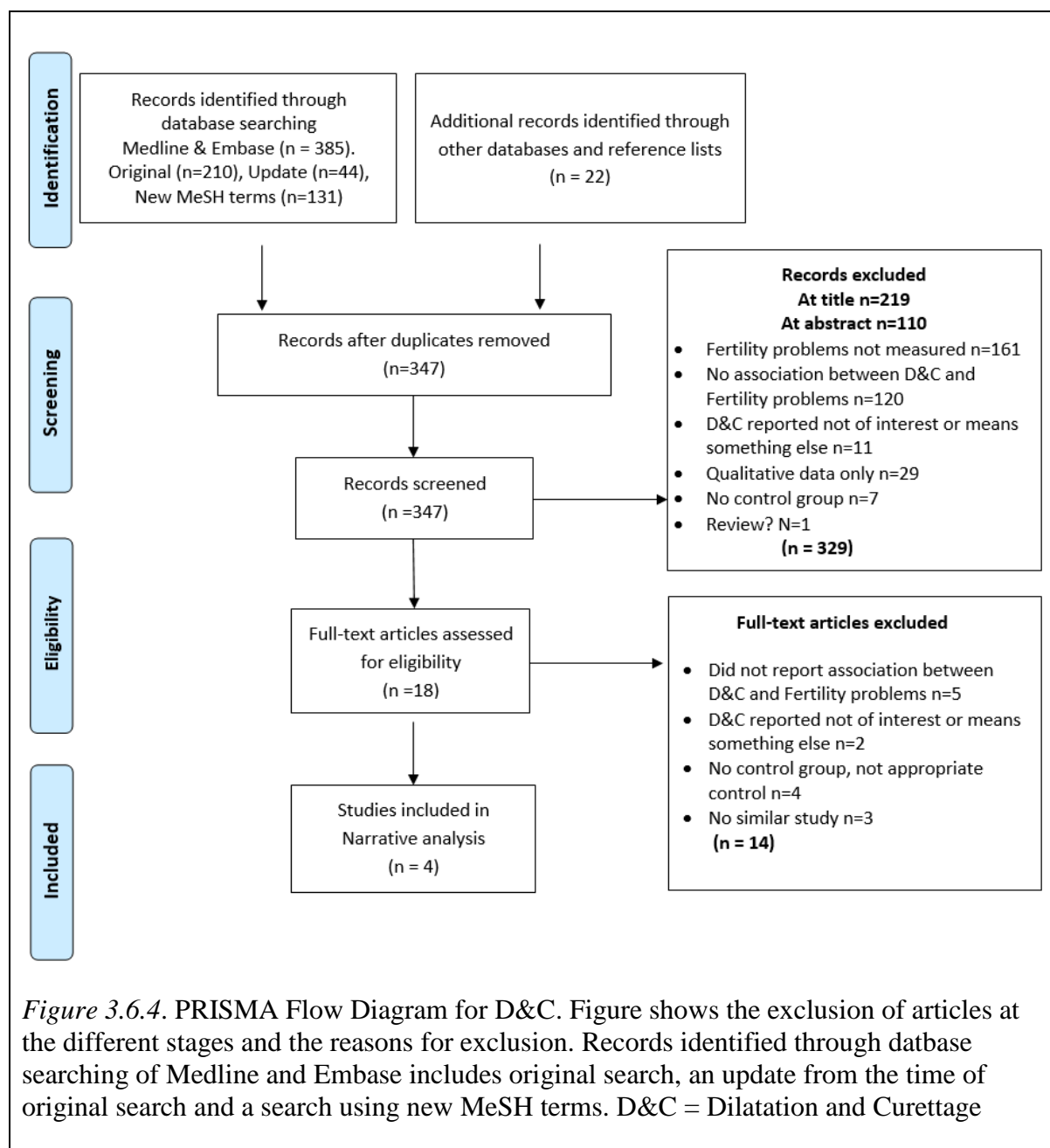
Data Synthesis and Analysis

As noted in General Methods (pp. 58), studies that could not be combined in a meta-analysis, due to different outcomes and methodologies, were reviewed narratively.

Results

Study Selection

Figure 3.6.4 shows the flowchart for number, reason and stage of exclusion of articles. A total of 347 records were identified (after duplicates removed) and most studies (281 of 347, 81%) were excluded because they did not report fertility problems or did not report on the association between D&C and fertility problems.



Of the 18 full text articles assessed for inclusion, four met inclusion criteria and reported on the association of D&C on future fertility. One of those four studies was obtained from the search of reference lists of the studies screened at full text stage (Ben-Baruch et al., 1991, retrieved from Hooker et al., 2014). Only studies reporting on ‘single’ D&C were found in the current search. The indication for D&C was different in all four studies: routine

investigation for infertility, spontaneous abortion (miscarriage), induced abortion and RPOC. The outcomes available in the included studies were: ‘PID, endometriosis and fibroids’ (Taylor, 1982), ‘gynaecological diseases and menstrual dysfunction’ (Sotnikova, 1986), ‘infertility’ and pregnancy (Ben-Ami, 2014; Ben-Baruch, 1991) following D&C compared with other management. The two studies reporting on long-term fertility outcomes of interest (infertility, pregnancy) could not be combined in meta-analysis because they defined reproductive outcomes differently, used different indications for the procedure and different comparators in the control groups.

Characteristics and Design of Included Studies

Table 3.6.2 shows selected sample characteristics of the four included studies. Only two included mean age at time of study that ranged between 28.6 and 30.5 years. Table 3.6.3 shows methodological characteristics of included studies. Three of the four studies were cohort design and one was cross-sectional, all data were collected from hospitals or clinic records.

The control groups were heterogeneous with two being untreated (Ben-Baruch, 1991; Taylor, 1982) and the other two being treated with hysteroscopy (Ben-Ami, 2014) or prostaglandins and/or vacuum aspiration (Sotnikova, 1986). The outcome ‘infertility’ was reported in two studies, but defined as mechanical infertility, included tubal damage and IUAs (Ben-Ami, 2014) and as 12 months of inability to become pregnant despite trying (Ben-Baruch, 1991).

Table 3.6.2.

Sample Characteristics Reported in the Four Included Studies

Study	Country	Sample (n)	N			Age ^a Women	
			D&C	No-D&C ^x		D&C	No-D&C
Ben-Ami, 2014	Israel	177 women	94 women	83 women	Mean (SD)	30.4 (6.3)	30.5 (5.9)
Sotnikova, 1986	Moscow	650 women	350 women	300 women	NR	NR	NR
Taylor, 1982	N/A	195 women	53 women	142 women	NR	NR	NR
Ben-Baruch, 1991	Israel	86 women	52 women	35 women	Mean (SD)	28.6 (6.1)	29.2 (5.0)

Note. ^x type of control group described in Table 3. ^a Age for women at the beginning of the study; ^b Unable to become pregnant after at least 12 months of unprotected intercourse; D&C= dilatation and curettage; NR= data not reported; SD=Standard deviation; Shaded study from search of reference list

Table 3.6.3.

Characteristics of the Design of the Four Included Studies

Study	Study design	Data collection	Study period	Control Group (no-D&C)	Indication for procedure	Fertility Problems: outcomes reported in primary studies
Ben-Ami, 2014	Retrospective cohort study	Hospital based	2000-2010	Hysteroscopic resection	RPOC	Infertility, time to conception in months, conception rate
Sotnikova, 1986	Retrospective cohort study	NR	NR	PG & vacuum suction	Induced abortion	Gynaecological diseases (e.g. salpingophitis, endometriosis), menstrual dysfunction (e.g. biphasic menstrual cycle, insufficient luteal phase)
Taylor, 1982	Cross-sectional study	Hospital based	NR	Did not undergo D&C	Routine investigation for infertility	PID, endometriosis and fibroid
Ben-Baruch, 1991	Prospective cohort study	Hospital based	1993-1988	Expectant management	Spontaneous abortion (miscarriage)	Infertility (attempted conception > 12) months after abortion or stopping contraception. Future pregnancy, miscarriage and normal delivery.

Note: D&C= dilatation and curettage; NR= data not reported; RPOC = retained products of conception; PG = prostaglandins; PID = pelvic inflammatory disease. Shaded study from search of reference list

Study Quality, Fertility Problems Outcome Measure and Bias

Table 3.6.4 shows the results of quality assessment. The majority of studies (3 of 4) were of high or average quality and only one study (Sotnikova, 1986) was rated lower quality as per quality assessment. D&C was adequately assessed, the non-D&C group (controls) were well defined, selected from the same population and exclusions were adequately reported in all but one of the included studies (Sotnikova, 1986). Comparability of at least one confounder in the D&C/non-D&C groups was reported in three studies and one reported on ‘obstetric history’. One study adequately evaluated and included confounders in the analysis (Ben-Ami, 2014). ‘Fertility problems’ outcome was adequately measured in only one study (Taylor, 1982), the rest were self-report. Response rate or loss to follow-up was not reported in one study (Sotnikova, 1986) and did not meet criteria in the other studies.

Table 3.6.4.

Quality Ratings for the Four Included Studies on the Basis of an Adapted Newcastle-Ottawa Quality Assessment Scale

Study	Quality Criterion						Overall rating ^g
	Adequacy of D&C (exposed) measure ^a Max 2 points	Adequacy of control (non-exposed), definition and selection ^b Max 2 points	Comparability of control ^c Max 2 points	Confounders adequately assessed Max 2 points ^d	Adequacy of outcome Fertility Problems measure ^e Max 1 point	None response rate or loss to follow-up ^f Max 1 point	
Ben-Ami, 2014	2	2	2	2	0	0	High
Sotnikova, 1986	0	0	0	0	1	0	Low
Taylor, 1982	1	2	1	1	2	NA	High
Ben-Baruch, 1991	2	2	1	0	0	0	Average

Note. ^a D&C was adequately assessed when hospital/medical records were available and sample was drawn from the same population (up to 2 points); ^b Controls were adequately assessed when selection was comparable to cases, and D&C was excluded properly in the control population (up to 2 points); ^c Comparability of controls was achieved if exposed/non-exposed were matched or adjustment during analysis conducted. One point for 'obstetric history' and one point for any other confounder (up to 2 points); ^d Confounders were adequately assessed if they were obtained from records or a blind interview, and one point was given if the same method was used for both groups (up to 2 points); ^e Fertility problems outcome was adequately assessed if independent or blind assessment was stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.) (up to 1 point); ^f Point given if same rate for both groups and <20% loss to follow up reported, NA: not applicable; ^g The overall quality rating was low (0 to 3 points), average (4 to 6 points), or high (7 to 10 points). Shaded from search of ref list

Narrative Results of Systematic Review

Four studies met inclusion criteria but could not be included in meta-analysis because of differences in methodology (indication for procedure, control group and outcomes measured), see Table 3.6.5 for summary of methodology and results of the four included studies. The first, compared impact on future reproductive outcomes of hysteroscopy versus D&C in women who had RPOC (Ben-Ami, 2014). This was a retrospective cohort study of the medical records of women who had undergone surgery to remove RPOC after a reproductive event (birth, spontaneous or induced abortion). Medical records or contact with the women who had undergone these procedures were used to ascertain the following reproductive outcomes: desire for pregnancy, became pregnant, time to pregnancy, new infertility problem, and gestational outcomes (delivery, abortion, placental complications, birth weight and gestational age at delivery). Reproductive outcomes were analysed for 177 women, however follow-up duration was not reported.

The hysteroscopy and D&C groups were similar in demographic characteristics, obstetric history and mode of conception preceding the RPOC. However, more women underwent hysteroscopy after birth and more women underwent D&C after abortion (unspecified if induced or spontaneous or both) to remove RPOC. The D&C group were more likely to comprise women who presented with abdominal pain and the hysteroscopy group were more likely to have had longer time from delivery/abortion to diagnosis of RPOC.

Results of this study indicated that the occurrence of an infertility problem was significantly higher in women who had undergone D&C, 23/94 (24.5%) than hysteroscopy 10/83 (12%) ($P= 0.034$). The aetiology of the infertility was tubal blockage and IUAs. The women in the hysteroscopy and D&C groups were equally likely to have a desire for pregnancy and to become pregnant. However, the time to pregnancy was significantly shorter

in women who had undergone hysteroscopy than D&C (7.4 ± 7 Vs 12.9 ± 16.8 months, respectively; $P = 0.037$). The fact that the average duration to pregnancy in the D&C group was more than 12 months, indicating that even the women who got pregnant did so after the 12 months, could explain why there are more infertile women but equal number of pregnancies in the D&C group.

Table 3.6.5.

Summary of Methodological Considerations and Results of the Four Included Studies

Study	Indication for procedure	Control Group (no-D&C)	Other factors	Follow up period	Results: Outcomes reported in primary studies	
					Significant difference	No significant difference
Ben-Ami, 2014	RPOC after birth, spontaneous or induced abortion	Hysteroscopic resection (HR)	More HR after birth and more D&C after abortion D&C group more abdominal pain (before procedure), HR group longer time from birth/abortion to RPOC	NR	More infertility in the D&C group Longer time to pregnancy (months) in the D&C group	Desire for pregnancy Achieve pregnancy
Ben-Baruch, 1991	Spontaneous abortion (miscarriage)	Conservative management (waiting)	Which treatment would be performed was decided by treating physician	28 months (range 12-68) in the D&C group 26 months (range 12-72) in the control group		Achieve pregnancy, miscarriage and normal delivery. Infertility (including existing and new cases)
Sotnikova, 1986	Induced abortion	Group 1- PG OR vacuum suction	Gynaecological history (e.g. age at menarche, genital inflammation) was reported	One year	More gynaecological diseases (e.g. inflammation of fallopian tubes, endometriosis) in the D&C group	

Study	Indication for procedure	Control Group (no-D&C)	Other factors	Follow up period	Results: Outcomes reported in primary studies	
					Significant difference	No significant difference
		Group 2 - PG		5 years	More menstrual dysfunction (e.g. anovulation, oligomenorrhea, insufficient luteal phase) in the D&C group	
Taylor, 1982	Routine investigation for infertility	Did not undergo D&C	Excluded women with history of PID, pelvic surgery abnormal menstruation	History of D&C or no-D&C	More PID in the D&C group	Endometriosis and fibroid

Note: D&C = dilatation and curettage; RPOC = retained products of conception; HR = Hysteroscopic resection; PG = prostaglandins; PID = pelvic inflammatory disease; NR = not reported.

The second study reported on the impact on future reproductive outcomes of D&C compared with conservative management (waiting) after miscarriage (Ben-Baruch, 1991). This was a prospective cohort study that included women who were treated surgically (D&C) within 24 hours or conservatively (waiting) after a spontaneous miscarriage. The choice of treatment modality was determined by the treating physician. Of the 114 women, 68 underwent D&C and 46 were managed conservatively (control). Only those who tried to achieve pregnancy were followed up, 52 of the 68 in the D&C group and 35 of the 46 in the control group. The following reproductive outcomes were reported: future pregnancy, normal delivery, miscarriage and infertility. Infertility was defined as not achieving pregnancy after 12 months of trying from the time of the miscarriage or after stopping contraception. The women were followed up on average after 28 months (range 12-68) in the D&C group and 26 months (range 12-72) in the control group.

Results indicated that the two groups were not statistically different in age, parity, gestational age and previous miscarriage. None of the women experienced short-term complications like prolonged bleeding. During follow-up, the differences in number of

pregnancies, normal deliveries, miscarriages and infertility were not statistically significant. Pregnancy was reported by 39 (75%) of the 52 women in the D&C group, and 27 (77.1%) of the 35 women in the control group. Normal delivery was reported by 22 (42.3%) of the 52 women in the D&C group, and 14 (40%) of the 35 women in the control group. Miscarriage was reported by 11 (21.2%) of the 52 women in the D&C group, and 5 (14.3%) of the 35 women in the control group. Infertility was reported by 13 (25%) of the 53 women in the D&C group, and 8 (22.9%) of the 35 women in the control group. However, a history of infertility prior to the miscarriage (treated in the study) was reported in 8 (61.5%) of the 13 infertile women in the D&C group and 5 (62.5%) of the 8 infertile women in the control group.

The third study reported on the effect of different methods of abortion on short and long-term gynaecological outcomes (Sotnikova, 1986). Two groups of women who had undergone termination of pregnancy using different methods (D&C, vacuum aspiration and prostaglandins) were followed for one year or five years. The study comprised two comparisons. In the first comparison 250 women were followed for one year, of whom 100 had had D&C only and 150 had had other procedures (vacuum aspiration or prostaglandins). The results showed that more gynaecological disease (i.e., uterus not returning to its normal size after delivery, endometriosis, inflammation or infection of the tube and ovaries, irregular uterine bleeding) was reported by more women in the D&C group (12/100 (12%), than women who had vacuum aspiration and/or prostaglandins, 4/150 (2.6%). The second comparison comprised 400 women who were followed for five years, of whom 250 had instrumental termination (D&C) and 150 had termination with prostaglandins. Results of the second comparison showed menstrual irregularity (e.g. anovulation, oligomenorrhoea) were reported by more women in the D&C group 20/100 (20%) than women treated with prostaglandins, 15/150 (10%) (Sotnikova, 1986).

The fourth study reported on the impact of D&C versus no-D&C on PID, endometriosis and fibroids (Taylor, 1982). This was a retrospective study of 195 women with unexplained infertility about to undergo laparoscopy and hysteroscopy as part of routine investigation, some of whom had also undergone D&C in the past as part of infertility investigation. The women who had not undergone a D&C in the past were the control group and the women who had undergone a D&C in the past were the exposed group. Women were excluded if they had a previous history of appendectomy, pelvic surgery, intrauterine contraceptive device usage, hysterosalpingography, episodes of PID or abnormal menstruation. Results indicated that the two groups were comparable in age, SES and duration of infertility. The group that had a history of undergoing D&C as part of past infertility investigation had significantly more cases of PID than the group that had no such history. Both groups were equally likely to have endometriosis and fibroids (Taylor, 1982).

Discussion

Principal Findings

There is a belief that D&C (single or repeated) as compared to other treatment modalities for examination or removal of tissue from the uterus compromises future reproductive ability. The results of the present study indicated that there is some evidence to support this belief but its reliability could be compromised by methodological inconsistencies of the primary studies. Consequently, there are some lingering questions about possible effects of the indication for the procedure and type of control group that could not be disentangled from the D&C procedure itself. Future research should aim to unravel these effects through integrity of control groups and indication for the procedure. Despite the lack of evidence in the current study of reduced pregnancy rate, and contradictory evidence regarding infertility after D&C, these results should not be considered to promote D&C as a safe procedure. Women should be informed of the potential increased time to pregnancy and

infertility that could occur as a result of undergoing D&C. It seems clear that D&C has an impact on women's future reproductive capacity as indicated by the increased time to pregnancy and new cases of infertility, gynaecological and menstrual problems. However, there are caveats to interpreting these findings: (a) the indication for performing the D&C was to remove RPOC, after spontaneous miscarriage, to induce abortion and as part of routine infertility investigation (Ben-Ami, 2014; Ben-Baruch, 1991; Sotnikova, 1986; Taylor, 1982, respectively), (b) three of the four studies were conducted more than 25 years ago (Ben-Baruch, 1991; Sotnikova, 1986; Taylor, 1982), (c) D&C was compared to different procedures in each study: hysteroscopy, conservative management, vacuum aspiration and prostaglandins or no procedure (Ben-Ami, 2014; Ben-Baruch, 1991; Sotnikova, 1986; Taylor, 1982, respectively).

The newer study (Ben-Ami, 2014) that showed a longer time to pregnancy and more new cases of infertility (TFI, IUAs) used hysteroscopy as the control group. Hysteroscopy differs from D&C not only in the way material is removed (see Figure 3.6.2) but also because D&C is blind and hysteroscopy allows for visual assessment, which maybe more accurate and therefore may lead to less complications. The difference between Ben-Ami (2014) and Ben-Baruch (1991) with respect to infertility could be due to difference in follow-up duration, because most women, achieve pregnancy after 24 months (100% of 'super fertile' and 'normal fertile', see Evers, 2002) and therefore if the follow-up duration is more than 24 months then this might reduce the number of women diagnosed as infertile and increase the number of women who achieved pregnancy. This appears to be the case in Ben-Ami (2014) because despite the longer time to pregnancy and more cases of infertility, there is ultimately no difference in the number of pregnancies, indicating that a longer follow up period might have been used, but this was not reported. In light of these caveats it could be that the effects seen are obsolete (e.g. the procedure is much safer than 25 . years ago and/or

it is no longer conducted as part of routine infertility investigation), or that effects are not permanent and resolve over time.

Justification for not including D&C in the FertiSTAT.

The results of the current review alone would lead to the conclusion that D&C should not be included in the adapted FertiSTAT because of the lack of pooled estimates regarding future reproductive outcomes like infertility, pregnancy and live births after single or repeated D&C. However, extant reviews and primary studies have tested a broader set of pathways that could suggest otherwise. The arm of the proposed pathway depicting the association between repeated D&C and IUAs (Pathway 4, Figure 3.6.1) has been reported historically (Schenker & Margalioth, 1982; Schenker, 1996) and corroborated with a recent meta-analysis (Hooker et al., 2014) that showed repeated (>1) D&C was correlated with increased IUAs (Hooker et al., 2014).

The arm of the pathway depicting the association between a single D&C and IUAs (pathway 3, Figure 3.6.1) was supported by a recent systematic review reporting more IUAs after a single D&C compared to hysteroscopic resection (Hooker et al., 2016). The high quality of the Hooker et al. (2014 and 2016) reviews and the fact that the current search did not produce newer primary studies to update the meta-analysis on repeated D&C and IUAs or the systematic review on single D&C and IUAs, indicates that these results are the most current statement of available evidence.

As noted in chapter 3.4, Asherman's syndrome occurs mainly as a consequence of trauma (e.g. termination of pregnancy, miscarriage and postpartum curettage) to the uterine cavity that results in IUAs, and has been reported to be associated with infertility (see Yu, et al., 2008; Schenker & Margalioth, 1982). Therefore, if D&C is more likely to lead to IUAs as evidenced by the Hooker et al. (2014) meta-analysis and the Hooker et al., (2016) systematic review then it is likely that D&C could be expected to lead to infertility via this path (Pathways 3 and 4, Figure 3.6.1) if it causes damage. The fact that the increased cases

of infertility reported in one of the primary studies (Ben-Ami, 2014) in the current review are tubal and/or IUA further corroborates the meta-analysis in Hooker et al., (2014).

Evidence for the other pathways suggested in Figure 3.6.1 come from primary studies or reviews published prior to 2000 and mostly indicates IUAs, gestational problems and secondary infertility, therefore, more data is required to validate these pathways. It is noted that cases where infection occurred and consequently PID are the only ones that lead to tubal infertility (Hogue et al., 1983). This was also corroborated by one of the included studies in the current review that indicated more cases of PID in women who had a history of D&C as part of routine investigation for infertility than those who did not (Taylor, 1982). However this evidence is over 30 years old, therefore replication is required to clarify if there were confounding factors that were involved such as septic conditions that increase the chance of infection and PID, that may no longer be relevant.

However, if we apply the ‘Bradford Hill criteria’ noted in the General Methods (pp. 55), we can see that three of the nine apply to the current review and enhance confidence in the causal relationship between D&C and fertility problems.

The criteria of ‘consistency’ was met because IUAs have been consistently found to be associated with D&C. The criteria of ‘specificity’ was met since the association of D&C with fertility seemed specifically related to IUAs which implies that there may be a more causal relationship between D&C and IUAs. The criteria of ‘biological gradient’ was met because the number of D&C procedures was found to be related to whether an effect was detected or not. The criteria of ‘plausibility’, ‘coherence’ and ‘experiment’ could be informed by biological evidence because that is currently lacking in the literature. Such evidence would enable a more accurate illustration of what aspects of the procedure itself or its repetition can cause damage, for example, is it the type of instruments used, the professional performing the procedure (level of training and experience), factors predisposing to the formation of adhesions (e.g., being more prone due to hormonal levels), clinical indication

(miscarriage, abortion, lost products of conception) and so on. It can be inferred from the application of the Bradford Hill criteria that inclusion of repeated or single D&C in FertiSTAT as a new risk factor could potentially increase prediction of fertility problems in LMIC.

Implications of Findings

Results of the current review indicated that D&C leads to more infertility and longer time to pregnancy, but has no impact on future ability to become pregnant, however, this is not based on pooled estimates. Nevertheless, an integration of recent empirical evidence and the application of the Bradford Hill criteria would suggest that the association between repeated and single D&C and IUAs needs to be considered in the adapted FertiSTAT and clinical guidelines for D&C and infertility investigation. One such recommendation would be that where preservation of future fertility is desired, D&C should be used sparingly and other alternatives such as hysteroscopy, should be considered especially when there is a history of past D&C and/or IUAs.

Strength and Limitations in Included Studies

The heterogeneity in study methodology, outcome measures and control groups in included studies affects the comparability of these studies, and the generalizability of the results of this review. Heterogeneity in fertility problems outcome (infertility, pregnancy rates, gynaecological and menstrual problems, PID, endometriosis, fibroids, IUAs), study design (cohort and cross-sectional) and data collection methods (different duration of follow-up after medical procedures and retrieving information from medical records), can affect the practical applicability of the results. Furthermore a lack of consistency in the definition of outcomes such as infertility (12 months trying compared with mechanical infertility) precluded the calculation of pooled estimates.

However, the quality of each study independently does not appear to affect the overall results of the review since the majority (3 of 4) of studies had at least moderate quality score.

Bias relating to the primary studies included selection bias, information bias and bias due to confounder. In hospital-based studies, the selection of participants based on hospital attendance can reduce the generalizability of the results. However, samples exposed to D&C can only be obtained from sampling in clinical settings because D&C is a clinical procedure. Bias due to confounder was a potential limitation of the studies included but it might not have been considerable given that matching the groups for confounders was reported in three of the four included studies and the most important confounder ‘obstetric history’ was included in one study. There could have been an unequal distribution of other confounders in the exposed and non-exposed groups but other confounders were not reported in the included studies. Additionally, the effect of confounders like clinical indication for the procedure, symptom presentation (abdominal pain prior to procedure) that could have influenced the relationship between D&C and fertility problems was not taken into consideration via either matching groups for confounders or entering them into analysis.

Future Research

Future research to disentangle the effect of D&C on fertility problems requires biological research, RCTs and prospective cohort studies to investigate the causal mechanisms that are involved. More biological examination of the uterus during and after the procedure (using technology like hysteroscopy and laparoscopy) could enable an examination of what aspects of the procedure are problematic. RCTs randomly assigning women to D&C and other treatment and/or prospective cohort study designs that follow women over time to measure both short and long-term outcomes should be performed.

To measure the effect of repeated D&C, a stratified RCT can be conducted where the sample all have a history of only one D&C, they are then randomly assigned to either an additional D&C or other treatment. In this case the D&C group would have in fact been exposed to more than one D&C. The factors that need to be considered in such research include: (a) clinical indications for D&C (e.g. miscarriage, abortion, RPOC), (b) nature of the control group (other procedures e.g. vacuum aspiration, prostaglandins or waiting/no treatment), (c) number of times (repetition) of D&C, (d) confounders like professional conducting the procedure (training and experience), post-operative care, obstetric history (e.g. previous pregnancy, miscarriage etc.), and (e) nature of the relationship between short and long-term consequences.

Ideally, an RCT that randomly assigns women to different treatment modalities (e.g. D&C, hysteroscopy, vacuum aspiration, misoprostol, and expectant/conservative management) stratified by clinical indications (miscarriage, abortion, RPOC, etc.) that measures both short-term (e.g. uterine bleeding) and long-term (e.g. IUAs, pregnancy etc.) outcomes, should be conducted. Measurements at baseline and follow-up should include: fertility problem outcome, obstetric history (e.g. number of previous pregnancies, miscarriages, abortions), demographics and other confounding factors (e.g. post-operative care). Follow-up periods should be well defined and not arbitrary (e.g. 12 and 24 months). An investigation of the association between the short-term outcome like prolonged bleeding and long-term outcomes like IUAs could elucidate the exact biological mechanism. For example, it could be that women who bleed more post-operatively are more likely to develop IUAs or that women who require further surgery (medical attention) are more likely to develop long-term consequences.

Alternatively, a longitudinal prospective cohort study could be conducted to follow women who have undergone D&C (once and more than once) with women who have not undergone any procedure and women who have undergone different treatment modalities (EXT, MED etc.). Research should also be directed at understanding the reasons for the incongruency between more IUAs and infertility but similar rate of pregnancy and to definitively ascertain if it is related to the repetition, the severity of the IUAs the development of Asherman's syndrome, the duration of follow-up or other reasons not currently known. Finally, it is imperative that after more such studies are carried out that an update of the review be conducted and pooled estimates calculated.

Conclusions

Fertility problems have been reported as a negative consequence of D&C in the literature but evidence to support this claim has been limited. Results of the integration of the current systematic evidence and empirical literature corroborated past evidence. A single D&C procedure was found to be associated with longer time to pregnancy, more mechanical infertility and more gynaecological and menstrual dysfunction. Repeated D&C may affect ability to become pregnant, but this appeared to be via the development of IUAs. Since IUAs do not always lead to infertility, and pooled estimates were not calculated for the other effects, inclusion of D&C at this time as an independent risk factor for fertility problems in the adapted FertiSTAT cannot be justified. It is important to note that this area of research should be re-examined due to the small number of available studies and the methodological shortcomings of the studies included in the systematic review.

Study 3.7 Additional endorsed risk factors: water-pipe smoking, vitamin D deficiency and cervical electrocautery

General Introduction

Three other RFs were endorsed in the survey of international doctors (Chapter 2, pp. 25): water-pipe smoking, vitamin D deficiency and cervical electrocautery (CE). The relevance of these factors was assessed in the present chapter.

Water-pipe smoking

The methods for using tobacco differ worldwide e.g. cigarettes, chewing tobacco, and water-pipe use, to name a few. According to the WHO, the impact on the human body is similar across methods of intake (WHO, Tobacco: deadly in any form or disguise, 2006). The water-pipe is a device used to smoke tobacco that involves passing the smoke through water before inhaling it (WHO, Tobacco regulation, Advisory note, 2015). There is a pervasive belief that smoking tobacco through the water-pipe is safe (WHO, Tobacco regulation, Advisory note, 2015).

The WHO advises that water-pipe smoking is as hazardous to human health as cigarette smoking. Specifically, a one-hour water-pipe session was assessed to be equivalent to inhaling 100-200 times the volume of smoke in a single cigarette (WHO, Tobacco regulation, Advisory note, 2015). Given this link and the strong evidence of the effect of smoking on fertility (Dechanet et al., 2011), conducting a systematic review on the impact of water-pipe smoking on fertility was not deemed necessary. However, an adapted version of the FertiSTAT should consider the inclusion of critical thresholds for water-pipe smoking to help a broader group of users recognise what level of consumption could be problematic for their fertility health. In the original FertiSTAT the critical threshold was smoking more than

10 cigarettes a day, consistent with empirical evidence (Axmon, Rylander, Albin, & Hagmar, 2006; Hull, North, Taylor, Farrow & Ford, 2000). Establishing comparable critical thresholds for other smoking methods (e.g., water-pipe, chewing tobacco) requires further study.

Vitamin D deficiency

Introduction

The Scientific Advisory Committee on Nutrition (SACN) in the UK recently published a report on vitamin D and health (SACN, Vitamin D and Health, 2016). The cut-off level of serum metabolite of vitamin D (the standard way to measure level of vitamin D) to protect musculoskeletal health should be above 25 nmol/L. It is noted in the report that the evidence for a causal relationship between non-musculoskeletal health and vitamin D is weak because it comes from observational studies only and the reported beneficial effects could be related to confounding or reverse causality. It is further noted that results of RCTs examining vitamin D supplementation for non-musculoskeletal conditions have produced inconsistent results (SACN, Vitamin D and Health, 2016). The Endocrine society guidelines endorse the following serum concentrations: (a) sufficiency: greater than 30 ng/ml, (b) insufficiency: 20-29.9 ng/ml, (c) deficiency: less than 20 ng/ml (Holick et al., 2011).

The motivation to evaluate the impact of vitamin D deficiency on fertility comes from a review of molecular level evidence in non-human animal and human studies suggestive of a role of vitamin D in supporting reproductive processes (see Lerchbaum & Obermayer-Pietsch, 2012; Anagnostis, Karras & Goulis, 2013). The aim of the current study was to examine whether there was evidence linking vitamin D deficiency and fertility problems.

Methods

The need for a review on Vitamin D and fertility was examined using the approach described in Figure 3.2 (step 2, pp. 59). A recently published review was obtained (Muscogiuri et al., 2017). The review summarised the literature on the potential impact of vitamin D deficiency on fertility. The review was quality assessed as per Figure 3.2 (step 3, pp. 59) and found to be current and of sound quality as critically appraised by the “Critical Appraisal of Systematic Reviews” published by the WHO (Abalos, Carroli, Mackey & Bergel, 2001), making an update redundant. Another recent review was obtained but not used this review was based on primary studies considering the impact of vitamin D levels on outcome of Assisted Reproductive Treatment (ART) only (Chu et al., 2017), therefore generalizations to individuals not in treatment would be limited. Consequently, the present chapter only summarizes (Figure 3.2, step 4, pp. 59) the evidence reported in the Muscogiuri et al. (2017) review and provides an assessment of the review methodology.

Results

Muscogiuri and colleagues (2017) reviewed molecular and epidemiological evidence for the relationship between vitamin D deficiency and female fertility. The outcomes examined were ovarian reserve, PCOS and endometrioses.

Muscogiuri et al., (2017) reviewed more than a hundred primary studies, however the exact number of studies and search methodology were not reported. Unfortunately, more details about methodology were not available despite contact with author. The evidence reviewed included molecular and observational studies, and interventional studies on the effects of vitamin D supplementation. Extant meta-analyses in the following areas were also examined: (a) physiologic effect of vitamin D level on female reproduction (molecular), (b) vitamin D level and ovarian reserve markers (molecular and cross-sectional), (c) vitamin D level and female reproduction in animal studies (molecular), (d) vitamin D level and PCOS

(molecular, observational and meta-analyses), (e) vitamin D level and endometriosis (molecular and observational), and (f) vitamin D supplementation and female fertility (guidelines and cut-offs, no primary studies).

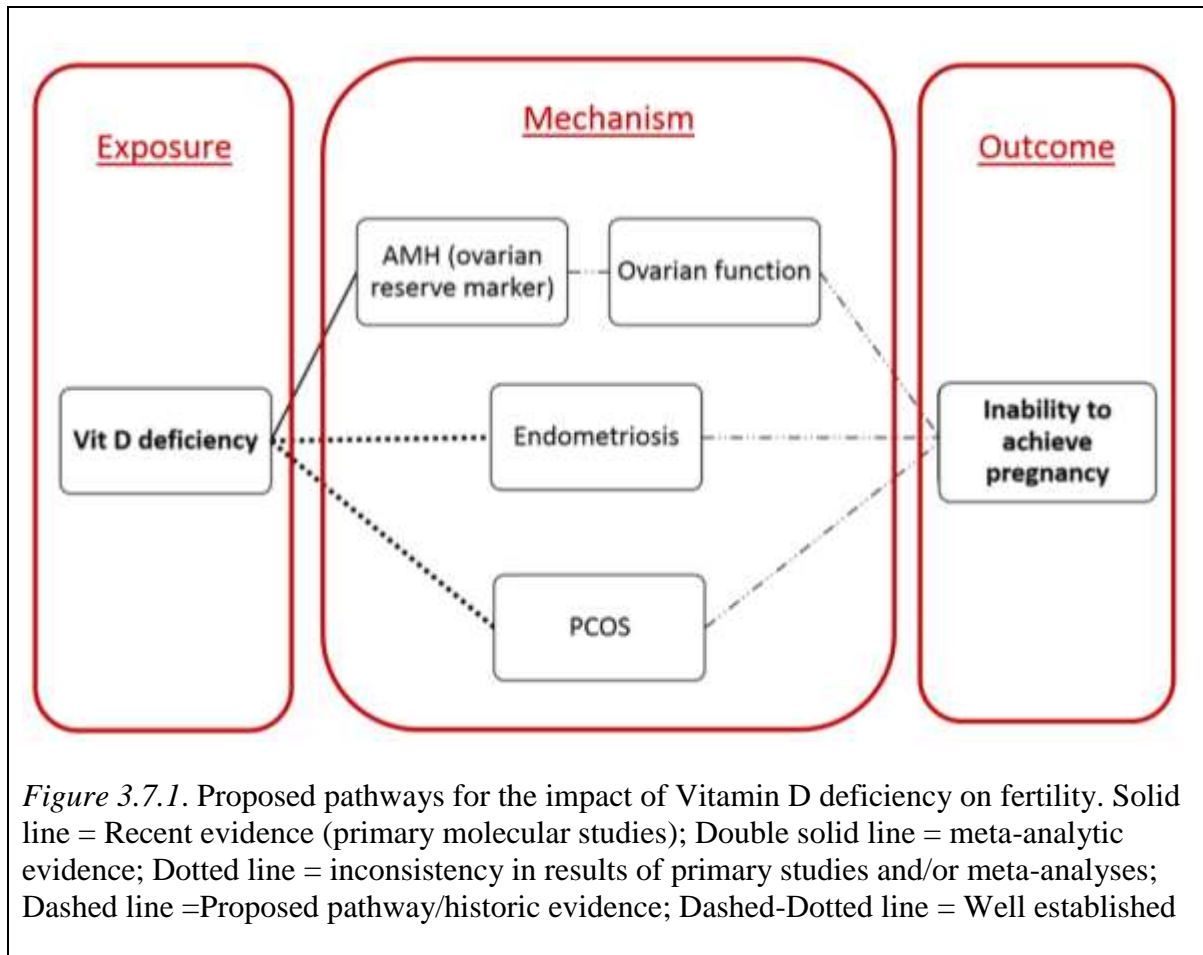
Three of the main conclusions reached were relevant to the current report. First, molecular and epidemiological evidence suggested that normal physiological processes in markers for ovarian reserve such as anti-Mullerian hormone (AMH) involved vitamin D (Muscogiuri et al., 2017). Second, there was inconsistency in results of studies reporting on molecular, epidemiological and meta-analyses regarding a relationship between Vitamin D level and PCOS diagnosis (Muscogiuri et al., 2017). Some studies reported an association between vitamin D deficiency and fertility problems in PCOS, and in PCOS with obesity populations, while others did not. One meta-analysis (Jia, et al., 2015) showed that women with PCOS had markedly reduced vitamin D as compared to controls, while another meta-analysis found only a non-significant trend of vitamin D deficiency in women with PCOS (He, Lin, Robb and Ezeamama, 2015). Intervention studies showed no impact of vitamin D supplementation in women with PCOS (Muscogiuri et al., 2017). Third, molecular evidence suggested that vitamin D could modulate inflammation and proliferation in endometriosis. In contrast, the epidemiological evidence for an association between Vitamin D level and endometriosis has been inconsistent. Muscogiuri and colleagues (2017) concluded that inconsistency in results for PCOS and endometriosis reflected methodological shortcomings in primary studies.

Discussion

Principal findings.

It can be inferred from the results of evidence summarized from Muscogiuri and colleagues (2017) that vitamin D is involved in physiologic reproductive processes, but its

involvement in PCOS and endometriosis is not confirmed. In light of this review, three potential pathways for associations between Vitamin D and fertility can be proposed, as shown in Figure 3.7.1.



Muscogiuri et al., (2017) proposed that sample size limitations and diversity in study design (observational, molecular) explained inconsistency in evidence for associations between Vitamin D and PCOS or endometriosis. However, other limitations could also explain mixed findings. First, the expression of the molecular relationship between vitamin D and PCOS or endometriosis (physiologic processes) may be more complex and therefore more difficult to measure than a simple direct relationship as seen in musculoskeletal health. The molecular role of Vitamin D in the utilization of calcium in musculoskeletal tissue is

simple and well established (Wolff, Jones & Hansen, 2008). Second, there could be confounding effects associated with Vitamin D level (e.g. better nutrition and health overall) that are not consistently measured or reported (SACN, 2016 report).

An application of the Bradford-Hill criteria (pp. 55) to the evidence in the Muscogiuri et al., (2017) review would indicate that the criterion of biological ‘plausibility’ is fulfilled through molecular evidence showing that vitamin D is involved in physiologic process in reproduction. The criterion of ‘coherence’ between molecular and epidemiological results is also met. However, the criterion of ‘consistency’ of results is not met, which would suggest that either the relationship between vitamin D deficiency and PCOS or endometriosis is weak or is mediated or moderated by confounding variables. Consequently, the mixed evidence presented thus far indicates that the inclusion of Vitamin D deficiency in the FertiSTAT would not be justified.

Implications of findings and future research.

Muscogiuri and colleagues (2017) recommend more rigorous research such as RCTs to study the effect of supplementation on fertility and studies that could help identify the exact molecular pathways. This research should examine the relationship between complex molecular processes linking vitamin D and PCOS and the outward expression of this relationship, studies should also ensure control of the primary confounders associated with Vitamin D.

A recommendation to have vitamin D supplementation to enhance/promote fertility is not yet warranted. Vitamin D supplementation has been recommended by the Endocrine society for all women between 18 and 70 years, and for pregnant and lactating women due to the depletion of vitamin D during these processes (Holick et al., 2011). These recommendations follow the proven beneficial effect of vitamin D supplementation for musculoskeletal conditions (of the muscles and skeleton) like osteoarthritis (Allan et al.,

2016), during pregnancy (Hollis, Johnson, Hulsey, Ebeling & Wagner, 2011; Kovacs, 2008) and for breast-feeding women (Kovacs, 2008). However, evidence for the benefit of supplementation for non-musculoskeletal health has not been as consistent, for example, supplementation does not prevent occurrence or reduce recurrence of cancer, or respiratory tract infections (see Allan et al., 2016). This inconsistency also seems to be the case with fertility problems because supplementation for PCOS was not shown to be effective (see Muscogiuri et al., 2017). The fact that vitamin D deficiency is correlated with numerous non-musculoskeletal medical conditions (see Peterlika, 2012) including fertility problems, but that supplementation is not beneficial (Allan et al., 2016), potentially suggests that the Vitamin D deficiency thresholds and optimal amount of supplementation required may be different than those for good non-musculoskeletal health. It could also be that for non-musculoskeletal conditions there are confounding factors such as overall nutrition and health mediating or moderating the impact of vitamin D levels. These findings need to be explored further to inform guidelines about whether and how much vitamin D supplementation to recommend for non-musculoskeletal conditions including fertility health.

The results of the Muscogiuri review and additional suggestions in this chapter would not affect the Endocrine Society recommendations because their supplementation is proposed for overall health and not specific to fertility. However, if new research can determine definitively that supplementation has a positive impact on women with PCOS or endometriosis or women at risk for these diseases then clinical recommendations should change to accommodate these new findings.

Cervical electrocautery (CE)

Introduction

CE is a gynaecological procedure that uses electricity to destroy tissue in the cervix (CE, “Cervical Cauterization,” 2017). It is used to treat inflammations, cysts and cancerous or precancerous tissue. Anecdotal reports from Egyptian doctors conducting CE suggested it was used to ‘cure’ infertility in LMIC (e.g., Egypt, Inhorn and Buss, 1993). Based on that anecdotal evidence Inhorn and Buss (1993) proposed that using CE to treat infertility could paradoxically cause tubal damage due to infection from septic conditions during the procedure. To test this prediction, a case-control study of 190 women in Egypt (100 infertile and 90 fertile) was conducted (Inhorn and Buss, 1993). The potential risk factors for infertility were extracted from medical and other sources and grouped according to the following categories: methods of ‘genital purification and hygiene’ (e.g. FGM, douching), sexual practices (e.g. number of sexual partners, use of prostitutes), ‘nutritional and consumption practices’ (e.g. obesity, diabetes, eating raw meat) and ‘iatrogenesis’ (e.g. postpartum infection, D&C, CE) which referred to past adverse reproductive events or biomedical procedures performed to treat infertility that could have unintended adverse effects on fertility. The authors proposed that these risks, as well as a composite of the latter category (all allegedly iatrogenic events and biomedical procedures) could lead to TFI. To test this hypothesis, cases with TFI and cases with other types of infertility were compared on this composite score. The results showed that CE was not associated with TFI in univariate analysis but in multivariate analysis, the ‘composite of iatrogenic risk’ was found to be associated with TFI (Inhorn and Buss, 1993). Important limitations of this work were a non-systematic data collection approach, poorly defined risk factors, and confounding of risks and outcomes. Data were obtained from medical records, research records and verbal reports from treating doctors at diverse times throughout the study introducing a high potential for bias. A clear justification for risk categories was not provided making it difficult to understand why proposed risks were perceived to be risks (e.g., genital depilation) or infer what shared causal

mechanisms could underpin risks within categories (e.g., depilation and female genital cutting). The risk categories also confounded potential risks (e.g., CE) with potential adverse consequences (e.g., infection) increasing the likelihood that categories would be associated with fertility problems but not individual risks.

Despite the lack of substantial evidence, it was thought that a review of CE was warranted due to the paper often being cited as evidence of adverse effects of CE, and endorsement of the procedure as a potential risk factor by 56% of the fertility experts in the cross-sectional survey (chapter 2, pp. 25).

Methods and Results

The need for a further review on CE and fertility was examined using the approach described in Figure 3.2 (step 2, pp. 59). In the present study, the search (step 1) resulted in no reviews, therefore the results of the search were screened (step 5). Screening resulted in no primary studies that reported on any association between CE and fertility. Additionally, there were no studies reporting on a potential impact or mechanism of action to indicate whether or how CE could affect fertility.

Discussion

Principal findings.

The only evidence for CE effects on fertility problems is the data provided in Inhorn and Buss (1993). This evidence is weak and does not warrant the inclusion of CE in the FertiSTAT.

Several explanations could be offered for the lack of further studies and reviews on CE effects on fertility. First, it could be that the Inhorn and Buss (1993) study was sufficiently compelling that the practice was abandoned to cure infertility or much improved

to address the problem identified (e.g., done in aseptic conditions) such that new research was not required. However, there were many important limitations to the Inhorn & Buss study that call into question the validity of their original conclusion or its possible effect on practice. Second, it could be that the Inhorn and Buss (1993) study was not disseminated among medical practitioners who could have been interested in carrying out more research because it was published in a social science journal. This could be true because many of the subsequent research citing Inhorn & Buss (1993) were from social science journals. Third, it could be that the premise for the Inhorn and Buss (1993) study was not generalizable, being based on anecdotal evidence from doctors in one clinic, and using CE for curative purposes not widely used in other clinics and countries. Finally, it could be that this practice is not done openly, therefore, researchers cannot study it.

An application of the Bradford-Hill criteria (pp. 55) to CE would suggest that only the criteria of ‘analogy’ (effect of similar factors e.g. other gynaecological procedures) could be met, but even gynaecological procedures like D&C have not been found to be definitively associated with fertility problems (Chapter 3.6). Therefore, the lack of evidence indicates that the inclusion of CE in the FertiSTAT is not justified.

Implications of findings and future research.

The need for research into the effects of CE is not known because its use in practice is not known (in LMICs). Therefore the recommendation of the current study is that more audit research about the use of CE in women presenting with fertility-related complaints should be conducted to determine need for research into effects. If this prevalence work reveals that that the procedure is still being conducted to ‘cure’ infertility then there should be more primary studies to test the hypothetical association with infertility because the existing evidence is too weak. Inclusion of CE in an adapted version of FertiSTAT could then be reconsidered.

General Discussion

Water-pipe smoking, Vitamin D deficiency and CE were endorsed in the survey of fertility doctors (Chapter 2, pp. 25) but none should be included as separate risk factors in the adapted FertiSTAT. Water-pipe should not be included as an independent RF but this method and its critical thresholds should be noted as one of the methods used to consume tobacco. Vitamin D deficiency should not as yet be included because of the lack of convincing evidence to determine definitively that vitamin D deficiency has an impact on female fertility. However, the existing evidence compels further research to investigate the potential nature, magnitude and confounding factors in this relationship. CE should not be included due to the lack of studies and therefore evidence to support its potential impact on fertility. The reasons for the lack of studies needs to be investigated as it is unclear whether CE is an abandoned procedure not worth investigating, or one that is routinely used but not investigated. Depending on the outcome of such investigation, the use of CE and the potential impact on female reproductive processes should be studied.

The examination of factors endorsed but not included in the FertiSTAT highlights the need to determine a strategy for how best to identify and assess new risks that should be further investigated for potential inclusion in FertiSTAT. In the present chapter, clinician endorsement, and historical and anecdotal evidence were used. However, for CE the evidence proved to be based on anecdotal hypotheses and no new evidence was found. For vitamin D, despite the extensive body of evidence, results proved to be inconsistent for an association with PCOS or endometriosis. It seems clear from the present and previous chapters that many reasons (anecdotal reports, primary studies and comparability to other risks) could prompt the need to investigate associations between a risk and fertility, but such reasons may not equally compel action. This diversity suggests a need to systematically utilize a method for the selection of risks such as that proposed by Ezzati and colleagues (2002), noted in

General Methods (pp. 58). For both vitamin D deficiency and CE an application of these criteria for risk selection would suggest that both are potentially modifiable. Additionally, for vitamin D there is data on risk levels for other diseases but not specific to fertility problems. A probability of causality and prevalence or hazardous nature of the RF were established from an aggregate of evidence for vitamin D deficiency but for CE these criteria were fulfilled only from anecdotal evidence and expert endorsement.

Therefore, from the present chapter it seems it can be concluded that investigation of a risk should only be pursued when there is compelling evidence that fulfils these criteria (or other selection criteria). This type of approach should be applied systematically and should become the standard prior to adaptation of current recommendations and tools.

Chapter 3

General discussion for all systematic reviews

Reducing risk has been a human preoccupation, and at the turn of the century the WHO emphasized that health promotion and communicating accurate information about risks has the potential to enhance people's adoption of healthier behaviors and lifestyle choices (WHO, World Health Report, 2002). Current patterns of fertility in LMIC, declining fertility rates, higher contraceptive use, lower maternal and child mortality, achieved through sustained progress on millennium goals suggest there now is space for a broader reproductive agenda that incorporates fertility health and the complex LMIC risk profile related to communicable and non-communicable diseases, cultural practices and overburdened healthcare systems. Some of these risks apply globally, such as HIV, while others might only have a regional impact, such as FGM/C.

Principal Findings

The original FertiSTAT was not found to be comprehensive for LMIC and therefore needs to be updated with risks relevant to LMIC. The RFs to be included in the adapted FertiSTAT were FGM/C, HIV, GTB, BV and CSG. The RFs that do not need to be included were D&C, Vitamin D deficiency and CE, at least until further evidence is accumulated. Information about the different methods for using tobacco should include critical thresholds for water-pipe smoking in addition to cigarettes. The RFs investigated were associated with fertility through multiple biological, behavioural and clinical pathways and meta-analytic results were consistent for the most part with past narrative reviews. The methodological rigor of the systematic review process adopted enhanced reliability, however, the small number of primary studies and inconsistencies in outcome measures were limitations.

To date many risk factors have been proposed in narrative reviews to impair fertility in women living in LMIC. The eight systematic reviews and five meta-analyses produced in this review showed that some but not all of these factors were associated with fertility problems. People living in LMIC could have a much more complex risk profile than is suggested by risks presented in the FertiSTAT or other awareness tools. A focus on prevalent risks in higher income countries or single risks could obscure the multifactorial risks to which people in LMIC could be exposed. This risk complexity should be reflected in fertility education and awareness tools, and the FertiSTAT should be adapted accordingly. What can and should be done about risk exposure needs to be determined within countries and regions utilizing a global health framework. The findings of multifactorial risk also reinforced the need to put fertility as an agenda in global health initiatives. Future research needs to determine what is the best method of selecting risk factors (RFs), methods to systematically evaluate pathways leading to reduced fertility, particularly more rigorous prospective designs or RCTs aimed at modifying risks (where possible).

Elaboration on main findings.

Table 3.3 provides a summary of the evidence reviewed, the outcomes reported, the number of studies included in each meta-analysis and the pooled effects estimate for those meta-analyses. As shown in Table 3.3, the RFs that would need to be included in FertiSTAT were FGM/C, HIV, GTB and BV to inform women of risk to ability to achieve pregnancy. CSG should also be included if the adapted FertiSTAT was to be used to inform women of fertility problems beyond ability to achieve pregnancy (e.g. stillbirth). As can be see the potential impact of these RFs is significant with largest effect size being a 9 fold risk in reduced fertility (i.e., GTB). These RFs have evidence from current meta-analysis, extant literature and met the Bradford-Hill criteria (except for HIV) providing strong evidence for their inclusion in the FertiSTAT. However, for FGM/C, HIV and BV data used in the meta-

analyses were calculated from case-control studies with clinical samples, potentially increasing sampling bias (Mann, 2003), but the conversion was methodologically sound (Kirkwood & Sterne, 2003, Chapter 16; Mann, 2003).

Table 3.3

Summary of evidence reviewed, outcomes reported, number of studies in each meta-analysis and pooled effects estimate.

RF	Evidence reviewed	Outcome reported	Number of studies included in MA	Pooled effect estimates
				OR (95% CI)/ Mean Difference (95% CI)
CSG	451 records retrieved, 24 studies included in MA	Time to first birth	2	MD 0.24 (-0.39-0.87) p=0.46
		Miscarriage	5	1.1 (0.93-1.30) p=0.25
		Never-pregnant	3	0.66 (0.45-0.98) p=0.04
		Childlessness	5	0.83 (0.67-1.03) p=0.09
		Mean # pregnancies	5	MD 0.40 (0.10-0.71) p=0.009
		Mean # live-births	7	MD 0.24 (0.05-0.43) p=0.01
		Stillbirth	5	1.28 (1.04-1.57) p=0.02
		Neonatal Death	4	1.57 (1.22-2.02) p=0.0005
FGM/C	244 records retrieved, 7 studies included in MA	Infertile > 12 months no pregnancy	2	1.17 (0.84-1.63) p=0.36
		Childlessness	3	1.22 (0.99-1.52) p=0.07
		Infertile 2 yrs (TFI)*	2	2.06 (1.03-4.15) p=0.04
HIV	741 records retrieved, 9 included in MA	Cumulative Pregnancy rate	2	0.36 (0.15-0.89) p=0.03
		Miscarriage	2	0.03 (-0.03-0.09) p=0.35
		Amenorrhea	3	2.44 (1.56-3.81) p<0.00001
		FSH >25 IU/l	2	1.51 (0.77-2.94) p=0.23
		Infertile > 12 months no pregnancy*	2	2.93 (1.95-4.42) p<0.00001
GTB	451 records retrieved, 5 included in MA	Infertile >12 months no pregnant	2	8.91 (1.89-42.12) p=0.006
		Amenorrhea	2	4.24 (0.23-78.14) p=0.33

RF	Evidence reviewed	Outcome reported	Number of studies included in MA	Pooled effect estimates
				OR (95% CI)/ Mean Difference (95% CI)
		Primary infertility	2	2.94 (1.89-4.37) p<0.00001
BV	184 records retrieved, 11 included in MA	Infertile > 12 months no pregnancy*	11	2.81 (1.85-4.27) p<0.00001
Narrative reviews				
D&C	347 records retrieved, 4 included in narrative review	Infertile > 12 months no pregnancy	1	Significantly more than hysterectomy group
		Time to pregnancy	1	Significantly longer than hysterectomy group
		Gynaecological diseases (e.g. inflammation of fallopian tubes, endometriosis) PID	1	More in the D&C than vacuum aspiration of prostaglandins. More in the D&C than no treatment group
CE	484 records retrieved, none met inclusion criteria	NA	0	NA
Vitamin D Deficiency	No review necessary	NA	0	NA
Water-pipe	No review necessary	NA	0	NA

Note. * = data calculated from case-control studies. RF = risk factor; OR = odds ratio; NA = not applicable; MA = meta-analysis; CSG = consanguinity; FGM/C = female genital mutilation/cutting; GTB = genital tuberculosis; BV = bacterial vaginosis; D&C = dilatation and curettage; CE = cervical electrocautery; PID = pelvic inflammatory disease.

Results of meta-analyses were also aggregated with extant evidence and used to construct a model that depicts how reviewed RFs impact fertility using outcomes reported in the primary studies, see Figure 3.3. Figure 3.3 shows that RFs could have multiple ways of impacting fertility. In Figure 3.3 the solid black lines are supported directly by meta-analysis from the current studies, while the dashed black line is supported by meta-analytic evidence from other studies and the grey lines are supported by primary studies (no meta-analytic evidence). However, primary studies do not systematically investigate all paths, therefore an incomplete picture is garnered from the literature.

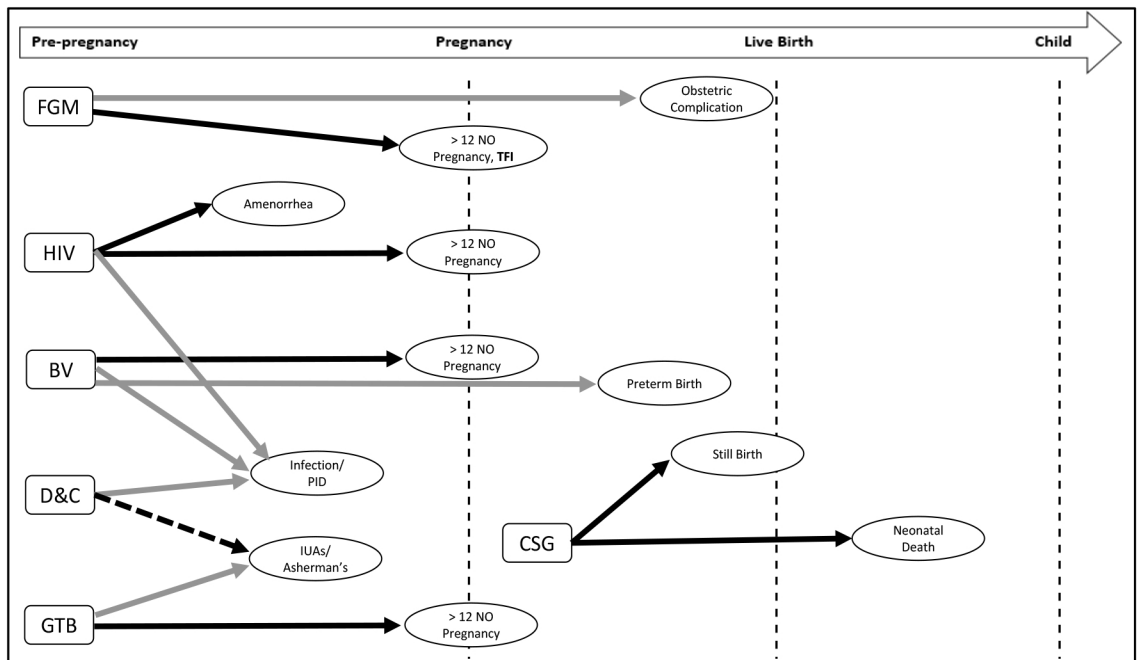


Figure 3.3. Association between risk factor and fertility problem indicator according to type of evidence and proposed timing of effect in reproductive process. Type of evidence = evidence from current meta-analysis (Solid arrow), evidence from previous meta-analysis (dashed arrow), evidence from primary studies or narrative reviews (shaded arrow).

Figure 3.3 reveals that women in LMIC have a complex risk profile, and effects could be additive and/or some RFs may interact with each other. One clear example is the well-established fact that the compromised immune system in HIV+ individual's increases the likelihood of other infections especially TB (WHO, Case Definitions of HIV, 2007). Therefore, HIV and GTB could potentially have an additive effect because each has an independent impact on ability to achieve pregnancy.

Some RFs appeared to have effects in only one part of the reproductive process, for example GTB appeared only to be associated with IUAs and inability to achieve pregnancy. This is likely due to the fact that GTB has been found to cause lesions in the female reproductive tract including the uterus and the tubes (Ahmadi et al., 2014; Chavhan, et al., 2004; Ghosh et al., 2011; Varma, 2008; Tripathy & Tripathy, 1998) that would preclude pregnancy. Therefore, impact further along the reproductive tract would not be seen. Other

RFs such as BV and FGM/C seem to have an impact at several points in the reproductive process. In the case of BV this could be due to the fact that infection that occurs before pregnancy and reaches the tubes will compromise ability to achieve pregnancy, while infection that occurs during pregnancy could damage the amniotic sac and lead to preterm birth. In the case of FGM/C, it is likely that the TFI occurs as a result of infection related to the more severe types of cutting where the anatomy is altered drastically. It should be noted that even if the cutting did not lead to infection, a women could still be at risk of obstetric complications if the altered anatomy made delivery difficult, which could lead to negative outcomes such as stillbirth as noted in the literature (Obermeyer, 2005; RCOG, 2015; Reisel & Creighton, 2015; WHO study group on female genital mutilation and obstetric outcome, 2006). Therefore, it can be inferred that timing and extent of exposure to RFs would affect fertility in different ways.

Some RFs have common pathways, for example HIV, BV and D&C were all related to infection and PID. Although with FGM/C there was no direct link with infections and PID (no data available), it can be assumed that would be the case because of the association with TFI. These risks could affect fertility due to the underlying trajectory or progression of infection producing that similarity, namely that any infection to the reproductive tract if left untreated could lead to PID, ascend to the tubes, or lead to tubal damage and therefore inability to achieve pregnancy (Ross & McCarthy, 2011; WHO, 2007, Global strategy for the prevention and control of sexually transmitted infections: 2006–2015). However, there were no consistent findings to suggest that infections always led to inability to achieve pregnancy. This is probably because the impact would only appear if the infection were untreated. Infections treated before they lead to PID would have no impact on the female reproductive tract and hence future ability to achieve pregnancy (Ross & McCarthy, 2011). Furthermore, not all infections lead to PID and not all cases of PID lead to tubal damage (WHO, 2007,

Global strategy for the prevention and control of sexually transmitted infections: 2006–2015).

Future research should ensure that data about treatment of infection is collected.

What can be clearly gleaned from Figure 3.3 is that the RFs that included infection, PID or TFI in their pathways (e.g. BV, HIV and FGM/C) were found to be associated with an inability to achieve pregnancy, affirming reports in the literature about infection being the leading cause of infertility in Africa and other LMIC (see, Cates, Farley, Rowe, 1985; Ericksen & Brunette, 1996; Leke, Oduma, Bassol-Mayagoitia, Bacha & Grigor, 1993; Odukogbe & Ola, 2005). One of the pathways of the effect of D&C noted in the literature was via infections (Hogue et al., 1983). However, these were historical data and it can be assumed that modern clinical care would be more aseptic than it used to be, thus not associated with fertility problems. The available evidence would suggest that whilst infection is a shared pathway its potential causes are multiple and clinicians need to be mindful of all of the risks for infection and not just STIs and unsafe procedures (abortion, delivery) as has typically been the case (Ericksen & Brunette 1996; WHO, Infections, pregnancies, and infertility, 1987).

The caveat to interpreting this diagram is that none of these results were obtained from RCTs. Therefore the causal nature of the relationships cannot be definitively ascertained. One way to address this limitation was using the Bradford-Hill criteria to determine the likelihood that there was indeed a causal relationship. Application of these criteria confirmed that a causal relationship is more likely in the case of BV, GTB, FGM/C, CSG and D&C in that order (more criteria met), see Table 3.4. However, there was no support for a causal relationship for HIV. The lack of support for HIV could be due to the numerous confounding factors such as abstaining from sexual intercourse, the use of barrier contraceptives or comorbid illness such as STIs, to name a few. Suggestions for improving research designs in HIV were made in Chapter 3.3. Additionally, future correlational

research on risk factors should be designed with consideration of how the design could inform these criteria.

Table 3.4

Summary of which Bradford-Hill Criteria were met for each of the six Risk Factors included in Systematic Review

Criteria	Risk Factor					
	CSG	FGM/C	HIV	GTB	BV	D&C
Strength				X	X	
Consistency				X	X	X
Specificity		X				X
Temporality	X	X				
Biological gradient	X	X			X	X
Plausibility	X	X		X	X	
Coherence				X	X	
Experiment						
Analogy						

Note. Bradford-Hill Criteria from Hill, 1965. CSG = consanguinity; FGM/C = female genital mutilation/cutting; GTB = genital tuberculosis; BV = bacterial vaginosis; D&C = dilatation and curettage

Strengths and Limitations of the Study

There were several review strengths that increased confidence in study findings. The review process used rigorous systematic review methodology that will be replicable. Two independent researchers duplicated screening and data extraction. Meta-analyses were possible for five of the nine RFs, not necessary for two RFs (vitamin D deficiency and water-pipe smoking) and not possible for only two risk factors (D&C no data, CE no primary studies). The use of best-practice guidelines in the design, assessment and reporting of methodology also helped bolster the trustworthiness of the results.

The decision to separate outcomes in meta-analysis also meant that more studies could be included in the reviews of each RF. This led to a more comprehensive review, with specific understanding of mechanism of action and identification of gaps in the literature,

which is the objective of systematic reviews (CRD, 2008). However, the small number of studies in each meta-analysis limited the generalizability of results.

The main limitation of the review process for all of the reviews was that sources of grey literature were not included, potentially increasing publication bias. However, assessment of publication bias for all meta-analyses using visual assessment of funnel plot asymmetry, trim and fill procedures and Egger's tests, did not alter the results.

Another limitation was how best to select RFs for the systematic review. The considerations used by the WHO (World Health Report, WHO, Chapter 2, 2002) and Ezzati et al. (2002) to select RFs were used (Chapter 3, General Methods, pp. 46) and were helpful in informing which RFs could be relevant to LMIC. However, the WHO and Ezzati et al. did not publish a decision rule for number of considerations needed to be satisfied to declare risk relevance. Due to the lack of cut-off points, the author decided that the more considerations were satisfied the more likely the RF should be selected. However, this decision rule ignores any weighting that could be applied to the risk. This was also the case for the Bradford-Hill criteria (Chapter 3, General Methods, pp. 55) used to ascertain the causal nature of the relationship. The validity of these assumptions can only be tested in future more controlled longitudinal evaluations.

In total 18 different outcomes that were markers of fertility problems were found and included in the reviews. This heterogeneity and additional lack of consistency with regards to measuring fertility problems and diverse research methodology adds complexity and limitations to making generalizations about the impact of exposure to said RFs. The implications of the heterogeneity in outcomes reported is that all primary studies could not be included in a single meta-analysis to evaluate the pooled estimate of the effect of exposure to any given RF on fertility.

Regardless of how rigorous the review process was results could only be as strong as the primary studies included. Three limitations of the primary studies were similar across RFs. First, was the recruitment at fertility clinics, possibly limiting selection to women at higher risk of infertility (applicable to GTB, FGM/C, BV). Second, the definition of outcomes, period of exposure or type of infertility were often not reported (applicable to CSG, BV, HIV). Third, was the lack of inclusion of confounders potentially moderating the effect of the risk. For example, the type of circumciser in FGM/C could be linked to an increase in the likelihood of infection and comorbid STIs (applicable to HIV and BV). Other limitations were specific to RFs, and reported in the respective chapters.

Despite limitations of the review process and of primary studies, the aggregation of available empirical evidence and the application of the Bradford-Hill Criteria to evaluate the causal nature of the relationship enabled conclusions to be made about the association between RFs and fertility problems. This was bolstered by the fact that the results of the current study supported evidence from narrative reviews for the most part. Exceptions were that past reviews and primary studies indicated more obstetric complications that could potentially lead to less live birth for FGM/C (Obermeyer, 2005; RCOG, 2015; Reisel & Creighton, 2015; WHO study group on female genital mutilation and obstetric outcome, 2006). However, in the current meta-analysis FGM/C was not found to be associated with more childlessness. Evidence in the literature indicated an association between HIV and more miscarriages and levels of FSH indicative of POI (Kushnir & Lewis, 2011) and GTB with more amenorrhea (Gatongi, 2005; Ghosh, 2011; Varma, 2008) but such associations were not corroborated in the current reviews. The lack of effect could be due to the methodological issues mentioned, but could also indicate genuine lack of association and reconsideration of the pathways through which these risks have effects.

Implications of Findings

Targeting communicable and non-communicable diseases is not only a priority to reduce the effects of these conditions but also their impact on childbearing and the morbidity experienced with that needs to be addressed. GTB was shown to have a nine fold increase in ability to become pregnant, HIV and BV both being global risks and found to have an almost threefold risk to inability to become pregnant within 12 months. While others that lead to smaller impact but are highly prevalent in some regions, such as FGM/C (Type II and III) a twofold increased risk of TFI (~90% in some African nations, UNFPA-UNICEF, 2014) and CSG, detrimental effects such as post-natal mortality (50% of marriages in some nations, Bittles, 2014).

The findings strongly support the movement toward having a more global understanding of risk for disease, and its extension to include a global view about RFs. This understanding would ultimately translate into more effective early detection of fertility problems in LMIC. Furthermore, it would allow health promotion to encompass culturally relevant health education and promotion. Clinical implications of these findings include education about the impact of these RFs that should be disseminated widely and in the most culturally appropriate manner. In addition to health promotion efforts, these results should be disseminated to clinicians who can have discussions with individuals about these RFs that can lead to better choices to protect reproductive capacity and to ensure that there is informed decision-making about fertility health.

The findings have specific implications for clinicians and women, and wider implications for the integration of fertility within the global reproductive health agenda. Awareness of the risks associated with reviewed RFs should be communicated to couples, especially where the threat of the RF is increased (e.g. high prevalence such as FGM/C in some countries, family member with TB, increased susceptibility to BV in black women and

smokers). Specifically healthcare practitioners and couples should be aware of the following. The closer the biological relationship between father and mother the more likely their progeny will inherit recessive genes that may be harmful (Bittles et al. 1991; Bittles & Black 2010; Hamamy et al. 2011; Hamamy, 2012) and genetic screening should form a part of routine pre-pregnancy examination. The potential impact of GTB, the latent nature of its effects, and TB screening should form a part of routine pre-pregnancy communication and examination. Menstrual disturbances and/or pelvic pain should alert practitioners to test for GTB, to enable early detection before irreversible damage occurs. For FGM/C, risks such as TFI need to be communicated and current guidelines should be followed to avoid labor complications such as fetal distress, emergency C-section and post-partum hemorrhage noted in the literature (Berg & Underland, 2013; Obermeyer, 2005; Reisel & Creighton, 2015; WHO, 2000), until pooled estimates of obstetric outcomes can be assessed. Current results concur with extant inclusion of HIV in pre-pregnancy care, emphasized by the WHO (WHO, Meeting report, 2012), and women need to be informed of the increased risk of infertility and amenorrhea associated with HIV. For BV, women should be advised to seek help for vaginal infections and health care providers should screen women for BV as part of routine gynecological examinations when risk for BV is present. For D&C women should be advised of the increased risk of developing IUAs and about safer options like hysteroscopy. For vitamin D, existing standard guidelines about supplementation that include all women between the age of 18 and 70 years, and for pregnant and lactating women (Holick et al., 2011) should be followed, as these apply to overall health of women. For water-pipe smoking, clinicians should advise women of the potential hazards of tobacco use regardless of method of use. For all RFs, practice guidelines should be updated regularly as more evidence is accumulated.

More general implications include how fertility should be integrated in the global reproductive health agenda because these RFs affect significant numbers of people. Even though each RF is a target for other campaigns (e.g., GTB, HIV, FGM/C), the impact of these RFs on fertility health unites these conceptually. The results can be used to inform a separate platform for fertility health in reproductive health or they can be used to inform separate platforms for each of these diseases, cultural practices or medical procedures. For example fertility problems can be communicated as possible sequel of GTB in TB campaigns or of FGM/C in anti-cutting campaigns. Alternatively a comprehensive holistic approach can be utilized such that clinicians and users would benefit more from an integration of fertility health and other campaigns in a comprehensive reproductive health approach. Whether fertility health is emphasized as a separate agenda within reproductive health or it is included within individual disease campaigns ultimately enhancing fertility awareness about RFs can potentially lead to more prevention of fertility problems.

Unanswered Questions and Future Research

The specific examples of what research needs to be conducted for each RF were informed from the gaps in primary studies and the models constructed and have been discussed in each RF discussion section. These included using more rigorous methodology like RCTs where that is possible and longitudinal cohort studies where RCTs would be impossible or unethical. It also encompassed the inclusion of well-defined and consistent outcomes and the inclusion of confounders. Future research should also target gaps in the primary literature regarding these RFs such that causal pathways are investigated in more detail, for example more molecular level investigations. The implications of the uncovering of the exact causal pathways would be that more specific clinical recommendations and best

practice guidelines could be established. Furthermore, research endeavors can be enhanced with the adoption of a more systematic approach to studying fertility health globally.

Future research should also be targeted at developing and updating standardized protocols to include the following. First, how to select RFs to be studied, for example existent criteria and models for the selection of RFs can be standardized with specific cut-offs. Second, how to examine the evidence for said RFs, for example through systematic review and meta-analysis of extant literature and the development of standardized methods for primary studies to include consistent outcome definitions. Third, how to apply and implement new evidence to clinical practice, guidelines and policies, for example adhering to minimum level of evidence that qualifies for best practice in the development and implementation of clinical care, guidelines and policies.

Conclusion

Nine RFs identified through literature search, survey and expert opinions (Chapter 2) were subjected to systematic review and where data permitted meta-analyses in the current chapter. Results lead to an understanding of the association of these RFs with fertility problems through an examination of outcomes available in the literature. These results indicated that FertiSTAT is not comprehensive for a global audience and should be adapted to include FGM/C, HIV, GTB and BV. Furthermore, if FertiSTAT is to be used to inform women about fertility problems beyond achieving pregnancy then CSG should also be included. The results were used to make recommendations for health promotion, clinical practice and best practice guidelines to ensure that providers and users are aware of the potential impact of these RFs and can then make the best informed decisions. Additionally, other fertility education materials should undergo a similar process of adaptation if they are to be used globally.

The reliability of the results was bolstered by the rigor of the systematic review process but was limited by methodological shortcomings of the primary studies found in the literature. The current study can be used as an example of how the systematic review process can only be as strong as the primary studies included. Therefore, the main recommendation would be for more rigorous and consistent standardized methodology of primary studies to reinforce extant literature. Overall the study also contributed to an understanding of the processes necessary in an exploration of risk for disease.

Chapter 4

Patient Interviews to Determine Need for Fertility Health Information and the Acceptability and Feasibility of Administering the FertiSTAT from the user's Perspective in a Sample of Sudanese Infertility Patients

Introduction

The cross-cultural adaptation of FertiSTAT for use in Sudan and the Middle East began with an exploration of the comprehensiveness of the RFs in the tool (Chapter 2, Study 2.1) and systematic review of identified risks (Chapters 3). This exploration was followed by an examination of the views of multiple stakeholders about the cultural acceptability and feasibility of implementing all versions of the adapted tool in the region (Chapter 2, Study 2.2). These activities underscored the need to include the perspective of potential users to provide a comprehensive investigation of the cultural sensitivity of the tool, which is the aim of the present chapter.

Fertility Knowledge in Sudan

It is important to note the lower literacy and education rates for Sudan to better understand how fertility knowledge fits within a broader education perspective. Education in Sudan is free and compulsory for children aged 6 to 13 years. In 2001 the World Bank estimated that primary and secondary school enrolment in Sudan was only 46% and 21% (respectively) of eligible pupils. It is also worth noting that although Sudan has 19 universities instruction is primarily in Arabic. That combined with the general lack of English language education limits the ability of people to obtain information from international sources such as the internet and English language publications. The population literacy rate,

which is the proportion of people who can read and write, is 70.2% of the total population (men 79.6%, women, 60.8%, see Library of Congress, 2004, pp. 65).

People in Sudan also have poor fertility knowledge. Anecdotal evidence drawn from a 1978 anthropological study conducted in Sudanese societies regarding reproductive and sexual beliefs (Nadel, 1978, as cited in Khalifa and Ahmed, 2012) suggested that Sudanese men and women believed many myths and misconceptions about reproductive and sexual behaviours. For example, sexual intercourse during menstruation can lead to venereal disease and sterility (Nadel, 1978). An example from this sample was that one female participant (age 38 years and university educated, residing in rural area) was unaware of basics of sexual intercourse, such as why the penis becomes erect. More recent research would seem to suggest that knowledge has not improved much. Al Safi (2007) reviews the literature in Sudan about reproductive knowledge, practices and the use of traditional healers. Al Safi (2007) reported that knowledge of reproductive functions such as the fertile period is vague at best. It is common knowledge that fertility is required in both partners and that the man's role in the process is to ejaculate his fluid within the woman's vagina. However, what actually occurs in the female after that is largely unknown (Al Safi, 2007). These results concur with other research on LMIC indicating poor fertility knowledge (Dyer, 2008; and Ali et al. 2011). Poor knowledge also extends to other areas of reproductive health such as family planning. In a study in rural Sudan, it was found that the unmet need for family planning was significantly associated with educational level of both partners (Ali & Okud, 2013). Unmet need for family planning was defined as those women who were not using contraception but who wanted to postpone or stop having children (Ali & Okud, 2013).

In addition to the challenges of low literacy and fertility knowledge in Sudan, there are cultural factors that impact understanding of fertility education. According to the latest (and only) data available, the average age of first marriage for women was 22.7 in 1993 and

21.9 in 2010 (United Nations, Department of Economic and Social Affairs, Population Division, 2015) and the average age of first births was 23.5 in 1993 (United Nations, Department of Economic and Social Affairs, Population Division, 2013). Therefore there is close correspondence between marriage and having a child. According to Al Safi (2007), in Sudan there are strong gender norms when it comes to reproductive health. Society places the blame of infertility and the burden of help-seeking on women, consequently women also bear the social stigma for childlessness and are obligated to accept divorce or polygamy as a result of infertility. Male contribution to infertility is rarely addressed and male competence should not be questioned which is especially in northern Sudanese society. Conventional knowledge in Sudan about male fertility assumes that male virility and sexual ability are indicators of fertility. Society expects that women should seek help and treatment, as well as bear the social stigma of infertility. This emphasizes the importance of increasing knowledge and awareness of infertility RFs among Sudanese women generally and women from low resource nations that share similar gender norms.

Views on infertility and IVF in Sudan also demonstrate stigmatization after treatment. In a prospective study Gaily et al. (2010) compared 96 babies born after IVF in Sudan and their mothers to controls conceived naturally using gestational assessment and an interview. The authors reported that 74.2% of couples that conceived with IVF/ICSI, hid the fact from their community (Gaily et al., 2010). The reasons cited by couples for hiding the fact included fear of child being ostracized (12.9%), to avoid social problems (21%) and to avoid family problems (19.4%) regarding blame for infertility and the cost of treatment (Gaily et al., 2010).

Cultural Sensitivity in Health Promotion

The importance of cultural appropriateness and sensitivity of interventions has been recognised as necessary in the adaptation of tools to new contexts. Cultural appropriateness and sensitivity are used synonymously in the literature. These concepts refer to the consideration of ethnic and cultural characteristics of a target population such as norms, values, beliefs as well as experiences (historical, social and environmental) in the design, delivery and evaluation of health promoting activities (Resnicow, Baranowski, Ahluwalia & Braithwaite, 1999). Making tools culturally sensitive therefore aims to go beyond merely adapting interventions that are targeted at a specific population via simple linguistic changes (e.g. modified language or translations) (Kreuter, Lukwago, Bucholtz, Clark and Sanders-Thompson, 2002; Betsch et al., 2016). Historically, cultural targeting has been used to achieve cultural sensitivity. Targeting involves modification of an intervention taking into consideration characteristics of the target population (Kreuter et al., 2002, Betsch et al., 2016). For example using the FertiSTAT in Sudan would require considering the literacy of the target audience so that if they are largely illiterate a self-administered tool would not work, and instead a provider tool would be required. The reason for investing in making tools culturally appropriate is that cultural sensitivity is linked with the impact of interventions especially when sensitivity is achieved through consideration of both the surface structure and deep structure (nature) of a population (Resnicow et al., 1999). Surface structure refers to matching interventions to the ‘observable’ nature of the target population (e.g. using similar language), while deep structure refers to the factors that impact on the behaviour of interest in the target population (e.g. social, environmental, historic factors) (Resnicow et al., 1999). Resnicow and colleagues (1999) noted that while surface structure may enhance acceptability and feasibility of interventions, deep structure is expected to determine the effect of such interventions. For example, in the latest Ebola outbreak in West-Africa, the WHO enforced guidelines for the proper disposal of corpses infected with Ebola including cremation

(Manguvo & Mafuvadze, 2015). Because these guidelines were in direct violation of traditional burial and funeral rituals of the target populations, they were not adhered to making the intervention ineffective (Manguvo & Mafuvadze, 2015). Instead, families of the deceased continued the traditional burial practices in secrecy and corpse collectors were bribed to forge death certificates to falsely certify that the deceased did not die of Ebola (Manguvo & Mafuvadze, 2015). In hindsight, the WHO should have targeted the management to the target population by taking into consideration the specific burial practices and convincing the people of the need to deviate from such practices to save lives (Manguvo & Mafuvadze, 2015).

Widely used and accepted guidelines for cross-cultural adaptation such as Guillemin et al. (1993) and Beaton et al (2000), provide thorough explanations of steps necessary for translation and cultural adaptation. However, these guidelines neglect to consider the deep structure proposed to be essential for effective impact of interventions because they mainly involve cultural targeting, as described previously. Kreuter et al. (2002) and Resnicow et al. (1999) suggest that adaptations could better link to deep structures via cultural tailoring. The difference between cultural targeting and cultural tailoring lies in the fact that targeting is aimed at the target population whereas tailoring is aimed at each individual within the target population and is based on characteristics of that specific person (Kreuter & Skinner, 2000). An example of cultural targeting in the FertiSTAT would be to use sensitive terminology when asking about sexual history (e.g. using the word ‘relations’ instead of ‘sexual intercourse’). In contrast, an example of cultural tailoring in the FertiSTAT would be to have instructions for the provider to gauge the level of religiosity of each user and based on that information to discuss the sexual history in a way most suitable to the religiosity of that specific user. Kreuter and colleagues (2002) suggest that although culture is shared amongst a target group the individuals within that group can have different levels of cultural beliefs

like degrees of religiosity (Kreuter et al., 2002). Govender (2005) suggested that health promotion efforts in Africa should not view culture as a barrier, rather cultural dimensions of health should be embraced within initiatives and interventions, consistent with the idea of culture as a building block of understanding (Betsch et al., 2016). Healey et al. (2017) conducted a systematic review of studies comparing health and mental health services with cultural adapted interventions and ones without such adaptations. Results of the review indicated that groups who received culturally adapted interventions showed better outcomes than those who received standard interventions (Healey et al., 2017). Specifically, groups that received culturally tailored interventions showed better outcomes, for example, lower subjective distress, more HIV tests, decreases in alcohol-induced problem behaviour, increases in daily fruit and vegetable intake (Healey et al., 2017).

Aim of current study

Results of the studies carried out thus far (Chapters 2 and 3) led to the conclusion that cross-cultural adaptation of FertiSTAT would require deeper understanding of user perspective. To achieve this understanding qualitative methodology was selected. Qualitative research can be used to ascertain subjective experience of individuals as it allows inquiry about and documentation and interpretation of human experiences (Patton, 2014). Knowledge generating contributions of qualitative inquires include but are not limited to the process of meaning-making, understanding peoples' perspectives and experiences from their personal stories and comparing cases to discover patterns and themes (Patton, 2014). According to Bowen et al. (2009) feasibility questions relating to whether the intervention can be used in a new target population (i.e. will it be found acceptable) and the most appropriate methods of delivering the intervention, can be best answered through qualitative research. These processes are necessary to identify modifications for the adaptation of FertiSTAT to address

cultural sensitivity and appropriateness informed by an understanding of the deep structures of Sudanese culture.

A thematic analysis was carried out to understand from the participants' perspective issues regarding the implementation of FertiSTAT. A semantic approach was used to understand the themes related to specific opinions on issues such as language used in FertiSTAT, and a latent approach was used to uncover the underlying motivations and ideas about the acceptability of FertiSTAT and related issues. Semantic themes are those that reflect explicit or surface meaning, while latent themes are those that reflect underlying ideas, assumptions and ideologies (Braun & Clarke, 2006). The meaning-making and subjective experiences with the tool as well as the patterns that arise from interviews was appropriate because to date experiences of people in Sudan with fertility education tools have not been documented.

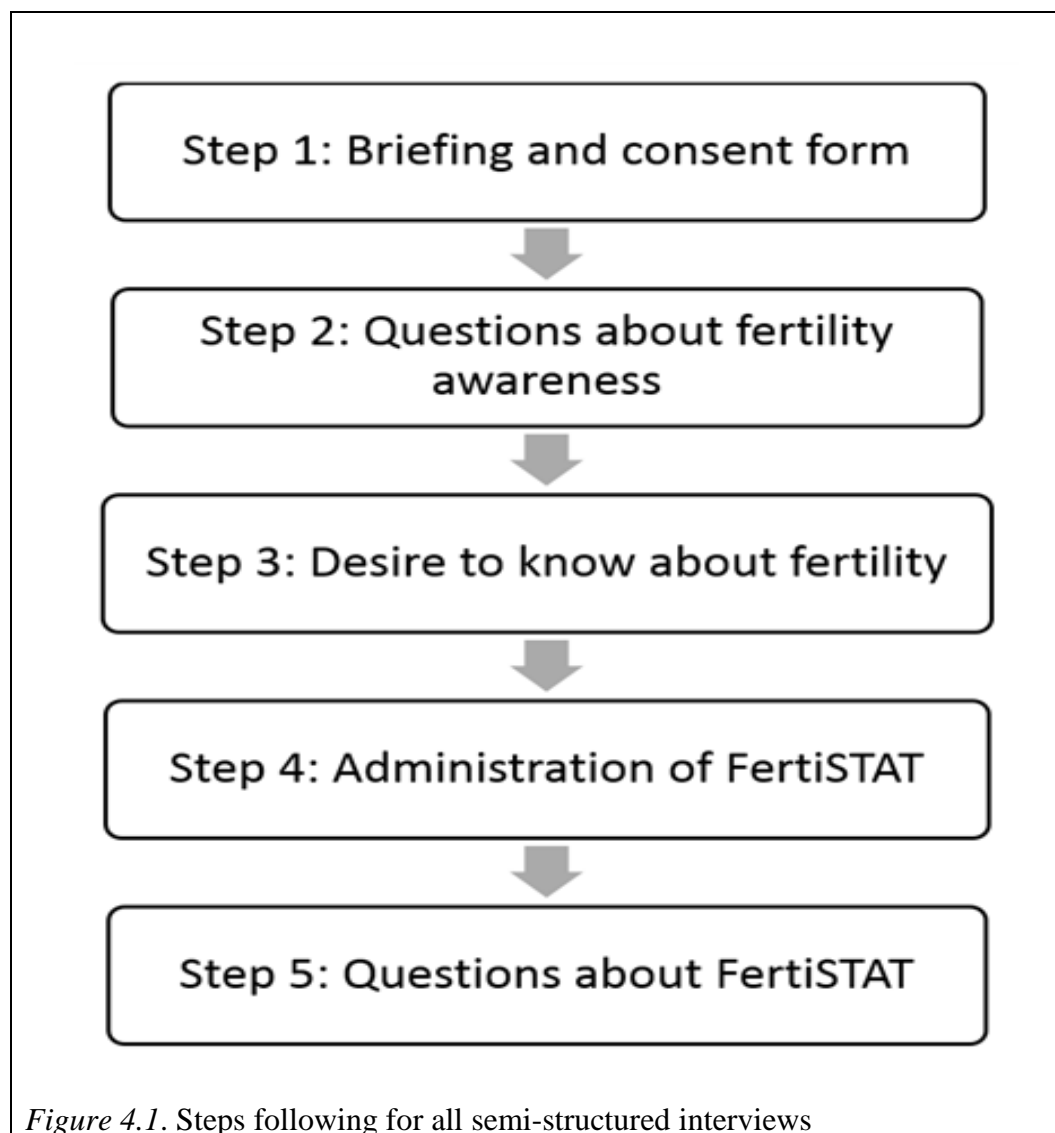
The first aim of this study was to elicit views on the need for fertility education in Sudan and the second aim was to assess acceptability and feasibility of implementing the adapted FertiSTAT among Sudanese people with infertility attending a private fertility clinic. Tackling these broad aims allowed consideration of the specific queries and recommendations of stakeholders from Study 2.2 (Chapter 2, pp. 36), such as exploration of topics perceived as taboo.

Materials and Methods

Study Design

Semi-structured interviews embedded within a cross-sectional pilot questionnaire study were conducted with Sudanese men and women experiencing fertility problems and attending a fertility clinic in an urban area. A background information form and the Arabic FertiSTAT were administered during the interview (see Appendix P for all materials).

The fertility quality of life tool (FertiQoL) was also administered for use in an independent study, therefore data on FertiQoL was not presented in this thesis. Figure 4.1 shows the stages of the interview component of the study. Interviews rather than focus groups were used to gauge the level of difficulty discussing sensitive topics like sex and drugs from each individual's perspective. Focus groups tend to be problematic because they can foster self-disclosure issues, limiting the understanding of personal thoughts, feelings and experiences (Hollander, 2004). Social desirability bias is the tendency to underreport socially objectionable activities and over report socially desired ones (Krumpal, 2013).



Participants and Recruitment

Patients attending a semi-private infertility clinic in Khartoum, Sudan were recruited from January to March 2017. Convenience sampling was used to recruit participants from patients attending a fertility clinic. Patients were recruited because the fertility topic would be of relevance to them, which would increase the likelihood of participation (Patton, 2014). There were no exclusion criteria. Ethical approval was sought and provided by the School of Psychology, Cardiff University (see Appendix Q). In this clinic (and most clinics in Sudan) the patients are seen on a first come first serve basis without prior appointment. Therefore, the patients spend many hours in the waiting room until they are seen by the doctor. This long waiting period provided an opportunity to approach patients while they were waiting. Of the 22 patients approached in the waiting room of the clinic, 20 (91%) agreed and completed the study. Recruitment continued until saturation of data was reached, and there was data replication and redundancy i.e. the point of diminishing returns in data was reached (Bowen, 2008).

Materials

Appendix P shows the materials for the study, which included the consent (including briefing), background information form, the tentative adapted FertiSTAT checklist, interview topic guide containing questions about the FertiSTAT and debriefing.

Background information: The 16-item Background Information Form was used to ascertain demographic and reproductive characteristics (e.g., age, past fertility history).

Fertility Status Awareness Tool: The tentative adapted FertiSTAT checklist was used to elicit understanding of fertility health issues (see Chapter 2, pp. 31). It was translated to Arabic (see translation section below).

Interview topic guide (questions about FertiSTAT): There were two components to the interview. First, participants were asked about their fertility knowledge. These questions concerned what they knew about the signs, symptoms and preventable causes of fertility problems and whether they knew when to seek help. Their desire for this type of information was also assessed. The second component of the interview concerned reactions to an awareness tool, specifically the FertiSTAT checklist. Participants were asked about acceptability of the tool referring to its topics, potential format of administration (e.g., specific format, setting, source and time required for administration), and finally, perception of the potential drawbacks, benefit and utility of the tool. Due to the fact that this was a semi-structured interview, some participant answers were responses to interviewer questions, while participants generated other answers spontaneously in response to more open-ended questions.

Translation

Materials, interview transcripts, and illustrative quotes were translated to Arabic, which is the national language in Sudan. RB in collaboration with local fertility experts in Sudan translated the adapted FertiSTAT checklist to Arabic. A bilingual Arabic-English linguist from a UK-based translation company (Business Language Solutions) verified the initial translation completed by RB. Interviews were audio recorded and RB transcribed and translated these. Translation of relevant quotes was checked via back-translation conducted by an independent research assistant Dr Kawther Mohamed (KM).

Procedure

Patients were approached in the waiting room and invited to participate in the study. Interested participants were briefed about the study. Those who agreed to participate were

asked to review and sign the informed consent form, including information about confidentiality, and were interviewed in a private room, individually or as a couple. Research assistants first collected demographic data after which RB conducted the interview questions. Interviews were conducted in a quiet, private room adjacent to the central clinic area. Interviews lasted approximately half an hour. At the end of the interview participants were thanked for participation and debriefed.

Data Analysis

RB and Dr. Emily Koert (EK) conducted thematic analysis (as coders) (Braun & Clarke, 2006). EK is a psychologist and post-doctoral researcher in the Cardiff Fertility Studies Research Group with clinical and research experience in fertility awareness and education. Dr. Koert has received extensive training in qualitative research and has conducted qualitative studies in infertility (e.g., Koert, & Daniluk, 2016; Boivin, Bunting, Koert, ieng & Verhaak, 2017). The coders followed these thematic analysis steps: (1) familiarisation with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes and (6) producing the report (Braun & Clarke, 2006). Using inductive coding, each coder derived initial codes from interview data for half of the participants. The other coder then reviewed the initial set of codes and the meaning of codes was discussed through analytic process memos. Coders discussed and reached agreement on whether each code communicated a unique meaning or fit with other existing codes. Each coder organized codes into main themes independently. The preliminary thematic groupings of codes were discussed between coders to deepen the analytic process, enhance trustworthiness of the findings and to ensure cohesiveness of each theme and consistency with the overall meanings in the dataset.

The use of parentheses within quotations (TEXT) indicates text added for clarity, while omitted text is represented using suspension points (...). Quotes are identified with the participant identification number (ID). Quotes are provided for latent themes when clearly illustrative of the idea, whereas when the idea was an integration of several quotes or analytic process memos, no illustrative quote was provided. Coders documented the thematic analysis process including analytic process memos and reflective notes creating an audit trail. To ensure trustworthiness of the findings, the data collection, analysis and presentation of findings was guided by best practice guidelines for qualitative research presented in the Critical Appraisal Skills Program (CASP; Critical Appraisal Skills Program, 2017) and Meyrick (2006).

Results

Demographics

One patient was briefed about the study, signed the consent form, asked to be excused and did not return to complete the study. Of the 20 patients who completed the study, three (15%) were men and 17 (85%) were women. The majority (65%, n=13) were educated beyond high school. The average age of the sample was 32.8 (SD=9.26, range 22-62) years, average duration of marriage was 4.9 (SD=3.58) years and average duration of infertility was 4.1 (SD=2.88) years. The reason for infertility was female factors only in 12 cases (60%), male factor only in two cases (10%) and both male and female factor in three cases (15%). The reason was unknown in one case (5%) and still not diagnosed in two cases (10%). Five (25%) women had previous pregnancies, but only two (10%) had live births, and one (5%) was currently pregnant (first trimester) as a result of treatment.

Results of Thematic Analysis

As shown in Table 4.1 thematic analysis resulted in six semantic themes, two latent themes and two meta-themes. For a more detailed record of quotes please see Appendix R.

Table 4.1.

Themes that emerged from thematic analysis from patient interviews in Sudan

Themes	Description of theme
Semantic themes	
Desire for fertility information	Fertility information that was desired and was it generated or endorsed
State of fertility knowledge in this sample <ul style="list-style-type: none"> • What is known • What is not known • Misconceptions/myths 	Current fertility knowledge, gaps in knowledge and misconceptions or myths about fertility
Benefits of fertility education <ul style="list-style-type: none"> • Perceived personal benefit (to self) • Perceived general benefit (to others) • Utility of the tool: addresses knowledge gap and encourage behaviour change 	Potential benefits of implementation of the tool to the participants (self), to people in Sudan generally (other) and what could be the potential uses of the tool
Specific suggestions for the tool <ul style="list-style-type: none"> • Content: taboo topics • Format: print Vs seminar • Setting: schools, home etc. • Source: doctor, specialist etc. • Timing: puberty, before marriage etc. 	Specific comments/suggestions about aspects of the tool and its implementation
Factors influencing implementation <ul style="list-style-type: none"> • Endorsed: <ul style="list-style-type: none"> ○ Personal preferences ○ Perceived benefit • Participant generated: <ul style="list-style-type: none"> ○ Acknowledging the benefit of education/information ○ The appropriate method of distribution ○ Persistence 	Factors affecting tool implementation <u>endorsed</u> by the participants Factors affecting implementation <u>generated</u> by the participants
Challenges and barriers to implementation <ul style="list-style-type: none"> • ‘Others’ will not accept taboo topics • Openness to health education in general and fertility specifically • Implementation may be dependent on level of understanding, knowledge, education and religiosity • Source not trusted 	Challenges and barriers to successful implementation of the tool

Themes	Description of theme
Latent themes	
Self-disclosure	Factors that affect self-disclosure, e.g. social norms, social desirability, demographics How issues of self-disclosure were resolved internally: self-other as a resolution for internal conflict of modern-traditional, cultures in transition, pull between modern vs traditional values When is self-disclosure important (practice vs research)
Understanding of being at risk	Aspects that affect our understanding of being at risk, e.g. demographics, previous knowledge and experience, culture (social norms, religion)
Meta-themes	
Compatibility with worldview	Compatibility of info with worldviews, social norms, beliefs and values that affect the acceptability and feasibility of using the tool in Sudan and the issues related to self-disclosure and understanding risk
Cultural tailoring	How the tool could be tailored to fit the a culture, i.e. according to gender, age, level of education or understanding and religiosity

Note. Tool refers to FertiSTAT

Semantic themes.

Six semantic themes emerged from the data. The first semantic theme was the desire for fertility information. The data provided evidence of unanimous endorsement of a desire for information about fertility. A few participants also indicated that they were actively looking for information, ID5: “yes, I’m currently searching (for information).”

The second semantic theme was the state of fertility knowledge in this sample. The participants’ level of fertility knowledge regarding signs, symptoms, preventable risk factors and when to seek help was gauged based on endorsement of information provided by the interviewer or generated by the participants. Most of the participants seemed to be aware of the impact of age on female fertility, ID20: “yes after 35 the chance is weak, very weak”, and to know that after a couple has been trying for one or two years they should go to the doctor, ID13: “I would say a year is good.” However, when participants were asked if they had fertility knowledge many stated that they didn’t, ID1: “I feel I have little information”, ID2: “No, I don’t know” and ID17: “no I didn’t know, especially the specific age I didn’t know

that.” There were also misconceptions/myths held by some participants regarding risk factors for infertility, ID13: “cleanliness and things like that” and isolating certain factors as the only cause of infertility such as, ID16: “(ovarian) cysts always.”

The third semantic theme was the benefits of fertility education. The benefit to self was expressed by most of the participants, ID2: “yes I would look at it, I would find it beneficial.” Most participants also reported benefit to others, ID17: “our society is in need of lots of raised awareness, A LOT!!” The utility of the tool was seen as both to addresses knowledge gaps, ID13: “to see where there are gaps and to fill them” and to encourage behaviour change, ID16: “from early on is better so I can avoid things like drinking too much coffee and tea and things like that.”

The fourth semantic theme was the specific suggestions for the tool which related to the content, best context for FertiSTAT and timing of its delivery to people. Endorsed or suggested changes about specific aspects of FertiSTAT that could influence acceptability and feasibility of implementation in Sudan were identified. The content of FertiSTAT could be an issue but suggestions for making it appropriate were provided. When asked about whether they thought the sensitive topics (sex, alcohol and drugs) would hinder acceptability, one participant stated, ID19: “maybe in the olden days maybe, but now it’s ‘aadee’ (normal)” and she noted that it would depend on how the provider was viewed: “if you introduce yourself properly in the beginning and they see you are a doctor, a professional,” then they would be more willing to accept these taboo topics. Most of the participants suggested that the interviewer just ask, using the Arabic word ‘aadee’ meaning normally, or casually, ID7: “people should talk about it ‘aadee’ (normally), because it’s for their benefit” and ID3: “a person should explain ‘aadee’ (normally) no problem.”

The best context for FertiSTAT referred to comments about format, setting and provider. All the participants endorsed a magazine version and some generated format

examples including seminars and print materials, although there was disagreement about print materials, ID19: “something printed the boys will not read it (...) if its lectures or seminars (...) they will accept it, they will listen, because a boy by nature wants to hear not to read.” The most suitable setting suggested by most participants was educational institutions (schools and universities), although some suggested that the home might be more appropriate, ID13: “I imagine the home to be the best context, I mean the most important role, one sees their father and their mother and how they are, it’s better that they show them.” The participants stated that the most suitable source to provide this fertility information was a doctor, a professional or specialist. Responses demonstrated that the source being perceived as knowledgeable, ID1: “a person who understands the issue” was more important than the profession or gender, ID19: “the real difference lies in whether the information was given by a specialist, not man or woman.” Some participants felt that a same gender source would be better, ID12: “it could be specifically for women, a seminar just for women so they can ask”. Several participants also thought that a family member, a parent or older sibling should convey this type of information, ID10: “your mother, older sister at home” and ID12: “the responsible ‘al gehat’ [entities], the mother.”

The timing and, relatedly, the most appropriate audience for using FertiSTAT were also discussed with specific suggestions provided. The majority of participants stated that the most suitable time to provide this information was at an early age. Specifically, participants stated puberty (same as ‘adolescence’ in Arabic) and the engagement period (before marriage) as the most suitable timings, ID18: “I think at puberty they should be made aware of these things” and ID19: “when they are in the engagement period, approaching marriage.” These suggestions were thought to be the time they can make changes to safeguard their fertility and to seek early treatment, ID16: “from early on is better so I can avoid things like

drinking too much coffee and tea and things like that” and ID15: “every girl MUST go and get checked out before she gets married.”

The fifth semantic theme concerned factors influencing implementation. This theme related to the factors influencing the acceptability and feasibility of implementing FertiSTAT in Sudan. Most participants felt that personal preferences would dictate whether FertiSTAT was acceptable, ID1: “it’s choices, you don’t like the page, you turn it.” It was also considered that the perceived benefits of the tool would influence its acceptability in Sudan, ID4: “the topic is not that difficult, it’s just information that one can benefit from.” And more generally, ID1: “clear and direct questions so that the answer is clear and direct, you benefit and I benefit.” Selecting the method of distribution would affect acceptability, ID14: “if it (FertiSTAT) is distributed right”. Finally, it was considered that acceptability would be improved through persistence in providing the information:

RB: so, you’re saying even if they say they don’t accept it we should give it anyway?

ID14: I told you, he will calculate it (risk level) in his head. He might think maybe this is right, he will do it himself (fill out the FertiSTAT).

The sixth and final semantic theme was challenges and barriers to implementation. Four potential barriers or challenges to implementing FertiSTAT in Sudan emerged. The possibility that ‘others’ would not accept taboo topics (sex with multiple partners, alcohol and drugs) was mentioned. Most participants stated that they would find it acceptable to talk about taboo topics but that ‘others’ would not. When asked if she would accept the materials ID5 responded: “yes acceptable” but when asked if others would accept it her response was different “some people will consider it and others will not”. Similarly, ID4: people may not accept these subjects, and:

ID1: cons, there are no cons for me, the topic is normal

RB: do you think people will respond authentically?

ID1: no (...) from the beginning you will get a sense of whether this person is willing to accept things, or not accept, for example, this sex question, most people will say 'enough I don't want to (continue)'

The lack of openness to health education in general and fertility specifically was expressed as a possible barrier by ID11:

...you will face difficulties, you will face unacceptance of the idea itself. I've done village work (working outside the capital city), acceptance of things like this was problematic for people. To communicate to them about family planning and to prevent circumcision of females and things like that, we faced problems, only God knows. Our problem is our customs.

Implementation was also seen to be dependent on level of understanding, knowledge, education and religiosity, ID14: "it will depend on their level of understanding, they may not accept it. Not everyone will accept, everyone has a different level of understanding" and ID1: "the religious one, in a religious way (...) God has forbidden certain things because they (the forbidden actions) can harm us".

Finally, the source might not be trusted and this could be a challenge, ID13: "it seems that it's always the case that if you trust the source (person) that the information is coming from, that's better. But if it comes from someone I don't trust, I will just leave him and go."

Latent themes.

Latent themes were the constructs perceived to influence the explicit content participants expressed. From this data set it was inferred that the latent themes (constructs) of 'self-disclosure' and 'understanding of being at risk' were influencing the behaviour of the participants.

The evidence for the latent theme of 'self-disclosure' comes from several observations. First, participants were unwilling to self-disclose about behaviours that were against social norms in Sudan (e.g. premarital sex in women). For example, RB noted that none of the 17 women reported sexual activity before marriage, which seemed unlikely.

Second, participants were

unwilling to self-disclose their true perceptions of the fertility information provided or the FertiSTAT and many mainly agreed with what the interviewer said.

Agreeableness, wanting to be sociable or aiming to please others also emerged because most participants just endorsed FertiSTAT as it was. For example, when asked “is there anything else you could add that you think would help us, or something to add about the information, or a specific way to talk about this topic?” ID1 responded: “no, your way is nice”. Agreeableness between spouses was also observed; as they did not contradict each other. For example, a wife and husband interviewed together:

ID19 (wife): yes it makes no difference, the real difference lies in whether the information is given by a specialist, not man or woman.

ID18 (husband): yes, I agree, the most important thing is that they have to be a specialist.

Agreeableness, was also expressed, for example by a participant who repeatedly denied any problem with the questions which were known to contain taboo topics:

RB: so these questions didn't bother you?

ID9: no.

RB: no problem at all?

ID9: no, no.

RB: OK, do you think there is something we can do to improve this work?

ID9: no, no.

RB: so you feel this is a good or bad thing, I mean it's beneficial, or it's just useless? What do you think?

ID9: no, no it's good.

Third, the participants who felt able to self-disclose (i.e. not affected by social desirability or agreeableness) were those that in Sudanese society would be allowed to violate norms, that is, those who would be perceived as higher up in the social hierarchy. From observations it was determined that male participants and more educated people could disclose or opine without worry. For example, an educated woman, ID19 (graduate level education): “OK you really have to write this (more research on varicocele) in the

recommendations!!” and an older male participant with female interviewer emphatically demonstrated more authority and confidence:

RB: so it's not a problem, for example we say 'this area, people should not talk about'?

ID8 (62 years old): it's WRONG not to talk about it!!

RB: so we should talk about all of this?

ID8: YES, YES!!

Another latent theme that seemed to be influencing observations about FertiSTAT was understanding of being at risk. Information in the data about how risk was understood in this sample and in general led to the identification of several factors that affected understanding of being at risk. One participant's understanding of being at risk seemed to be informed by a combination of religious doctrine and previous knowledge of disease transmission:

ID7: everyone knows what can harm them and can help them, and they are still doing the (behaviour that is) wrong, like, for example, sex, they know it can transmit diseases but they still do it. They use protection and say 'I won't get a disease'. They know everything but they try in different ways to do things, but this thing (premarital sex) is haram (forbidden by Islam) and wrong.

The coders agreed that the understanding of being at risk could differ by age, for example younger people appeared to feel more invincible, as this quote from a person reflecting on their younger self before marriage expressed, ID1: “before marriage I didn't have information about sexual education. Before marriage, I felt like I didn't want to educate myself.” There appeared to be gender norms about behaviour and risk taking too, as demonstrated:

ID14: They should show this to the men too, so they don't say it's just from the woman (the fertility problem), they have to, they have to know it, this thing especially, boys will be boys, so you know boys can have relations (sex) as much as he wants before marriage and stuff, and then he comes and then, I mean after marriage he will have repented to God (no longer engages in sex with anyone other than his wife) and they have no problem (no extramarital affairs).

These quotes reflected the participants' understanding that although social norms allow premarital sex for men this still may be a risk, thus the understanding of being at risk was partially based on gender.

The data demonstrated that understanding of being at risk could be informed by previous knowledge, information (e.g. media, socially) and personal experience of infertility specifically (disease specific) or medical issues more generally (across disease): RB: "was the information beneficial? And was there any information you were not aware of before?" ID6: "yes, useful, I've seen it before". Another participant expressed that had she known about the signs of fertility problems like irregular periods, she would have sought treatment when she developed these problems, rather than waiting after marriage, ID15: "every girl MUST go and get checked out before she gets married, to get herself checked, I had problems with my period, and I was not bothered with it."

Understanding of being at risk was also informed by what is forbidden by social norms, laws or religious doctrine, ID1: "God has forbidden certain things because they can harm us." Understanding of being at risk can also affect behaviour, as one participant outlined ID13: "So, knowing about this, awareness about such things especially here in Sudan, here the girl won't go to the doctor no matter what. For example, if her period is late she should find out, if her period she could have a problem, go to the doctor."

Meta-themes.

In addition to the two latent themes, two meta-themes emerged, 'compatibility with worldview' and 'cultural tailoring.' The participants' responses demonstrated that if health information/education was perceived to be compatible with a personal worldview (values, beliefs, philosophy, e.g., Islamic teaching) then it was more likely to be taken up and assimilated. When information was not congruent with personal worldviews, it could be disregarded or discredited. For example, several participants expressed the general Muslim

society belief about the value of knowledge, ID5: “this is a type of education and (education) is not wrong.”

Participants stated that Islam forbids some of the risk factors for infertility identified in the FertiSTAT. One female participant explained, ID1: “sex outside marriage is haram (forbidden by Islam), God has forbidden certain things because they can harm us.” However, another participant shared that people in Sudan continue to engage in haram behaviours despite being forbidden:

ID7: And I tell you something, in this day and age, they all know, they know wrong from right. And they are doing the wrong (regardless). Everyone knows what can harm them and can help them. And they are still doing the wrong, how, like, for example, sex, they know it can transmit diseases but they still do it. They use protection and say ‘I won’t get a disease’. They know everything but they try in different ways to do things, but this thing (premarital sex) is haram (forbidden by Islam) and wrong.

RB: but if she is unwilling to accept; this information is important for them to know, they should know that unprotected sex with multiple partners can affect their ability to have kids in the future, it can lead to diseases that can infect the spouse, so how can I convey this information, what if I get a really shy or religious patient?

ID1: the religious one, in a religious way, that sex outside marriage is haram (forbidden by Islam), God has forbidden certain things because they can harm us, you reach her at her level of understanding; each person at their level of understanding.

ID13: yes, early is one year, some people wait 4 or 5 years to get tested, no I mean you have just wasted time like this. It’s better that they find out, so that even if God did not will it (meaning you can’t have babies), you can separate. Sometimes there are people that God gives them (a baby) with someone else, it was not meant to be here (in the first marriage).

Another meta-theme that emerged from the data was the idea that tailoring the health messages of an educational tool like the FertiSTAT to make them more compatible with the user's worldview would make the tool more acceptable. For example a female participant provided the following ideas in order to reach people (ID1) "Each person at their level of understanding":

ID14: (...) printed materials, posters, pamphlets that can reach the mum or the aunt at home, they read it. People who can't read (illiterate) can get it at the mosque, you give the information to the imam (priest) and tell him to convey. This way the people at the mosque will know something and the mums will get the printed material.

Tailoring was suggested according to several factors. First, religiosity, some participants stated that information should be tailored to the extent of the individual's religiousness, ID1: "the religious one, in a religious way, that sex outside marriage is haram (forbidden by Islam), God has forbidden certain things because they can harm us." Second, gender, some participants stated that when the source of information was of the same gender as the audience this might lead to more acceptability of the materials:

RB: Ok, so is it better from a woman or a man?

ID10: it's better from a woman of course!

RB: so it's better if a woman comes and talks to the girls and she can tell them and show them?

ID10: why not, a man, for example, I can't ask him questions, but you are a woman like me so I can ask you questions.

Third, to the education or level of understanding, several participants stated that information should be provided at the individual's level, ID1: "you reach her at her level of understanding, each person at their level of understanding" and ID14: "people who can't read (illiterate) can get it at the mosque, you give the information to the imam (priest) and tell him to convey."

The coders' integration of semantic, latent and meta-themes with the aims of the study lead to the development of the map depicted in Figure 4.2. As demonstrated in Figure 4.2, the semantic themes of desire for more information, benefit of fertility education and the state of fertility knowledge all seem to inform the need for fertility education. The figure also shows the challenges and solutions regarding the acceptability and feasibility. Challenges include the latent themes of self-disclosure, understanding of being at risk and the perceived unacceptability of materials by 'others'. The potential solutions include the semantic theme related to the specific tool changes noted in the data as well as the meta-themes of tailoring to be compatible with world views.



Figure 4.2. Map of themes and how they apply to aims. Need = need for fertility education; Acceptability and feasibility of administering FertiSTAT; Challenges = factors viewed as potential challenges to implementation of FertiSTAT; Solutions = solutions to enhance implementation of FertiSTAT; Desire = desire for fertility education; Benefit = perceived benefit of fertility education; State = state of fertility knowledge; Understanding Risk = Understanding of being at risk; Tool specifics = changes to the tool; Worldview = compatibility with worldview; Tailoring = cultural tailoring

Discussion

Principal findings

Although the FertiSTAT checklist was in Arabic and included culturally relevant items such as FGM/C, meaning it was culturally targeted, issues of acceptability remained.

Thematic analysis of the data indicated that for this sample fertility education was perceived to be necessary and beneficial. FertiSTAT would be acceptable and its implementation would be feasible only if challenges were addressed in a culturally sensitive manner.

Challenges included the difficulty of accepting communication about sensitive topics such as sex and drugs, issues of self-disclosure and understanding of being at risk. Approaches to address said challenges included changes to the format of delivery (e.g. all women seminars) that would reduce the social hierarchy and could facilitate self-disclosure. In addition, cultural tailoring to make materials compatible with individual worldviews was inferred to be a solution both to generate a personalized understanding of being at risk and to enhance acceptability of sensitive topics.

Elaboration on main findings.

Results showed a need for fertility education stemming from a lack of fertility knowledge among people in Sudan that was consistent with reports in the literature both in developed (Bunting, Tsibulsky and Boivin, 2013) and developing countries (Ali et al., 2011; Ola, Aladekomo and dan Oludare, 2010). The data confirmed that this Sudanese sample wanted to know more about their fertility as inferred from their expressed desire for information and given their current knowledge was fairly basic and they had significant knowledge gaps and believed common myths about fertility.

It was inferred from the data that the tool as presented would only be acceptable and feasible if it was compatible with the Sudanese culture. This need was congruent with reports in the literature emphasising that successful implementation of health promotion in culturally diverse settings hinges on achieving accurate cultural sensitivity in health messaging (Betsch et al., 2016; Kreuter et al., 2002; Resnicow et al., 1999). Beyond cultural targeting it was also inferred that the materials needed to be compatible with the each user's specific level of cultural attributes. One way to achieve this compatibility, ascertained from the results, was to

tailor the materials with an understanding of the deep structure of the society to fit each user's specific level of socio-cultural factors such as religiosity and education, consistent with reports in the literature (Kreuter et al., 2002; Resnicow et al., 1999). Some challenges were identified and specific changes to the tool were suggested to tackle these challenges.

Challenges to implementation.

There were three main challenges ascertained from the data. First, its potential unacceptability to some members of Sudanese society, second, variable willingness to self-disclosure and third, complex ways of understanding of being at risk.

The main challenge garnered from the data was that although all the participants expressed that they accepted the materials for themselves, some felt that other people in Sudan might not accept the tool. This self versus other dichotomy could reflect several processes. First, it could be that people were not willing to disclose openly their own views of the tool and projected objections onto others. This would not be surprising given that in Sudan being agreeable, cooperative and helpful is valued. Second, this dichotomy between acceptability for 'self' and 'other' could be a manifestation of the pull between modern and traditional values inherent in cultures in transition, as is the case for Sudan. Participants most often highlighted the self-other dichotomy when considering the acceptability of addressing taboo topics in the tool. An example of this would be that many of the participants accepted the need to ask about taboo topics for themselves but stated that 'others' might not be as accepting. In this way, the participants could convey a modern view of self while projecting the negative 'traditional' beliefs onto the 'other' as a way of maintaining aspects of both tradition and modernity within one's persona. Therefore, it appeared that this sample may be liberal and willing to engage in premarital sex (more modern), but yet still feel hampered in disclosing sexual history due to fear of being judged according to traditional social norms forbidding premarital sex (laws and religious doctrine). These findings highlighted the need

to address such dichotomies when tailoring health promotion tools to individual preferences and worldviews (Kreuter & Skinner, 2000).

The second challenge was willingness to self-disclose less favourable aspects of the self. Results suggested that Sudanese users might not be as willing to self-disclose as they could be about their lack of knowledge or exposure to particular risks, congruent with the literature (Gerbert et al., 1999; Krumpal, 2013). This unwillingness to disclose seemed to be mainly due to worry about creating bad impressions with others (spouse, doctor). The consequence of lack of self-disclosure in clinical contexts is obvious, for example not being forthcoming about smoking, alcohol consumption and other issues that can impact fertility were noted by fertility doctors as challenges to accurate diagnosis of a fertility problem (Five little white lies that can impact fertility, 2016). It can be inferred that self-disclosure to the provider matters most when disclosure will lead to research or clinical findings that can be skewed, however there does not appear to be a difference in self-disclosure to a researcher or a physician (Gerbert et al., 1999). Given that self-disclosure may be uncertain in formats that lead to social desirability bias, for example survey and interview (Krumpal, 2013) the question then becomes, 'to what extent can self-disclosure impact research, clinical and educational outcomes for participants and providers?' The answer would depend on the purpose of the survey or interview, such that research purposes would suffer immensely from lack of self-disclosure as would clinical screening because recommendations based on false or missing information would in turn be inaccurate or incomplete. Self-disclosure is critical in clinical practice because it could lead to more accurate management and in research because results of said research could be used to inform clinical practice and guidelines (Gerbert et al., 1999). Self-disclosure can also be viewed as a challenge to health education since it would reduce the provider's assessment of perceived comprehension in the user (Krumpal, 2013). When self-disclosure is about being forthcoming with information giving to the

provider then some suggestions made by the participants in this study could help, for example an all-female seminar and same gender source. An example of areas where self-disclosure may be less essential are educational programs, as one participant stated: “a person, even if he is taking (drugs) he will tell you this is none of your business. So when he reads it even if they don’t accept it, they will still know the levels (critical thresholds) the effects and such.”

A third challenge to risk communication was perceived understanding of being at risk. It has been reported that to avoid hazards such as smoking people need to understand what it means to be at risk (Weinstein, 1999), and this perception of risk is influenced by several factors including psychological and cultural factors such as attitudes and values (Boholm, 1998; Sjöberg, 2000). It was inferred from the data that understanding of risk was moderated by person characteristics further reinforcing the need for tailoring materials to individual needs. The data in the current study speak to the recognition of personal risk or susceptibility being influenced by several features like age and gender but also by social norms and culture, congruent with the literature (Boholm, 1998; Sjöberg, 2000; Weinstein, 1999). It could be inferred from the data that youngsters are perceived to be uninterested in health education possibly linked to the idea of lack of perceived risk associated with age. The data suggested that perception of risk might be related to gender, for example, infections affect women only, and therefore sexual behaviours of women only are important. This was congruent with reports in the literature of women perceiving themselves as more at risk and men perceiving themselves as less at risk (Boholm, 1998; Fiuncane, Slovic, Mertz, Flynn & Satterfield, 2000). Several participants emphasized the inclusion of men in fertility education that is congruent with the importance of addressing men in gender neutral health education noted in the literature (Östlin, Eckermann, Mishra, Nkowane and Wallstam, 2006). Integration of gender into health programs (inclusion of gender norms and taking into account gender-based

inequalities) has been reported as a way to achieve positive reproductive outcomes (Boerder *et al.*, 2004; Robertson, Douglas, Ludbrook, Reid and van Teijlingen, 2008).

Another example highlighting the complexity of understanding risk is the common belief that unmarried girls should not seek out treatment by a gynaecologist even if they are having menstrual problems. From RB's experience as a Sudanese woman, this could be due to two factors: young women do not understand that this is a risk and therefore do not seek help and the pervasive cultural/societal assumption that unmarried girls are not having premarital sex and thus they are not at risk and gynaecological services are not necessary. This could reflect on the one hand the lack of knowledge about non-sexually related gynaecological diseases that can affect fertility (e.g. anovulation) and on the other hand it reflects a denial about premarital sex in girls. One participant discussed that had she known about the impact of menstrual problems on fertility, she would have sought treatment before marriage (pp. 232). This showed that knowing the importance of seeking help early might help safeguard future fertility, demonstrating that a new understanding of being at risk could ultimately lead to behaviour change.

Potential solutions to identified challenges.

Implementation of a culturally sensitive version was not perceived to be a significant challenge. Participants generated multiple proposals for where and how the tool could be implemented for example information leaflets or same sex seminars, targeting adolescents and those about to embark on marriage in schools and universities. These results were in line with recommendations of the Sudanese Federal Ministry of Health that health promotion should focus on community-based interventions (e.g. homes, schools, workplaces, markets, hospitals, colleges, villages and cities) and that schools were a setting where child, parent and teacher involvement could enhance health promotion efforts (Elsubai, 2007). Many participants stated that a doctor would be the ideal source to disseminate the information,

because they were perceived to be knowledgeable and trustworthy, congruent with the idea that doctor-patient communication could be viewed as a basis for motivation, reassurance and support (Betsch et al., 2016) could be one

Need for compatibility with worldview.

The findings suggested that people might be more willing to accept health-based educational materials that are compatible with their worldview. This meta-theme related to the idea that information that is perceived to be compatible with ones worldview, beliefs, values and social norms is more acceptable and can be integrated into ones understanding of a concept. It may well be that participants found the materials to be acceptable because in Muslim society, “knowledge is good”, as one participant stated when discussing the sensitive and taboo nature of the topics, “this is a type of education and this is not wrong”. Findings demonstrated that when materials were perceived to be compatible with worldviews this enhanced the acceptability of fertility education, for example “sex outside marriage is haram (forbidden by Islam), God has forbidden certain things because they can harm us.” On the other hand if information is not congruent with one’s worldview then this information is simply discarded or discredited. Making materials compatible with users’ worldviews would depend on the materials being, culturally sensitive and personally relevant. One way to achieve both would be through cultural tailoring and personalization of the materials.

Need for cultural tailoring to be compatible with worldview.

The participants’ recommendations underscored the need to tailor materials to the individual in order to be congruent with their abilities and views. The idea that enhanced effectiveness is related to congruency between the message and each user’s cultural attributes has been suggested in the literature (Betsch et al., 2016) and is consistent with the HBM (Rosenstock, 1990). Betsch and colleagues (2016) stated that “cultural congruency” i.e. equivalence between user’s cultural characteristics and health message led to better outcomes

and that choices about messaging should be consistent with informed values. The fact that the information about congruence and tailoring emerged from the data organically without actively being sought, confirms the legitimacy of such claims in the literature (Kreuter et al., 2002; Govender, 2005; Timmerman, 2007).

According to the HBM individuals may be less inclined to apply risk to themselves due to the erroneous belief that they are unsusceptible to risk (Abraham & Sheeran, 2005; Rosenstock, 1966, 1990). Thus if a person does not perceive themselves to be at risk then they would not act to change their risky behaviour or to seek help (Rosenstock, 1990). Accordingly, they will lack appropriate motivation to adhere to doctor's recommendations to reduce risk behaviours or to seek help (Abraham & Sheeran, 2005; Rosenstock, 1966, 1990). Personalized information as opposed to generic health messaging can increase the likelihood that people will reduce risk behaviours (Noar et al., 2007; Sohl & Moyer, 2007). Therefore, to enhance motivation to change behaviour, health messages need to be made personally relevant and of direct impact on a person's life (Noar et al., 2007; Parkes et al., 2008; Petty & Cacioppo, 1986). The perception of personal risk is not enough to produce behaviour change because people may discredit the information in an attempt to decrease the fear evoked by the message (Witte & Allen, 2000). Therefore, fertility education interventions need to go beyond personalization, to provide specific guidance about the action necessary to decrease risk (Witte & Allen, 2000).

Behaviour change is not only affected by perceived risk but cultural variability can potentially influence actions after understanding personal risk. Different cultures have diverse interpretations of what to do when at risk, for example 'western educated industrialized rich and democratic (WEIRD) societies' may be more willing to act on risk to take action and seek help (Henrich, Heine and Norenzayan, 2010), but in other cultures risk may be interpreted as a state of being with no feeling of being compelled to take action. In Islam,

taking care of one's health is encouraged, both in the hadith (Prophetic sayings) and the Quran. The Quran makes it explicit that one should not contribute to self-harm or destruction and the prophet Mohamed stated that people should seek treatment for disease because God has created a medicine for all ailments, except old age (Assad, Niazi and Assad, 2013). Given this strong belief in protecting one's health and seeking treatment it may well be that in Muslim societies like Sudan, a perceived risk status would compel behaviour change and help seeking. The influence of culture and religion on the interpretations of what to do when at risk is an illustrative example emphasizing the need for cultural targeting and tailoring. However, even an understanding of personal risk and religious doctrine may not be enough to lead to behaviour change as suggested by one of the participants who said that even though people know premarital sex is wrong and harmful they continue to do it (pp. 323), as in all cultures. Effective behaviour change would be a challenge in this field as it has been in others (e.g., cardiovascular disease).

The FertiSTAT provides both the personalized information and the guidance about how to change behaviour (Noar et al., 2007; Parkes et al., 2008; Sohl & Moyer, 2007). However, cultural adaptation of the FertiSTAT needs to take a few extra measures, such as understanding the factors influencing behaviour change in that culture and the potential barriers and benefits of change in that culture. Once these factors are understood they can be used in the most culturally and individually relevant way. Activities of adaptation of the FertiSTAT reported thus far have followed methods of cultural targeting to address cultural sensitivity. However, the current study underscored that effective implementation of the FertiSTAT needs to go beyond cultural targeting that reflects an understanding of deep structures. Successful implementation of the adapted version of the FertiSTAT must include cultural tailoring based on each individual's characteristics or level of cultural attributes to achieve maximum impact and not just personalisation to their level of risk.

It can be concluded from an integration of the data and the literature that successful health messaging that leads to behaviour change needs to evoke a perception of personal risk, provide guidance about what to do to address this risk, be culturally tailored to be congruent with each user's worldviews and address barriers and benefits of behaviour change.

Strengths and Limitations

The main strength of this study was the methodology followed by the coders and the adherence to best practices guidelines of qualitative analysis (Braun & Clarke, 2006; CASP, 2007; Meyrick, 2006), which included independent coding, double checking and discussion of coding, and thematic analysis with ongoing documentation of the analytic process which created an "audit trail". Issues of researcher bias and reflexivity were discussed between coders in order to enhance the trustworthiness of the findings. Another strength was the fact the interviewer and coder RB was from the target population which is consistent with 'Constituent-Involving Approaches' that suggest that the inclusion of indigenous staff leads to awareness about cultural features that go beyond the obvious observable characteristics such as language and dress (Kreuter et al., 2002).

Given that this was a very small Sudanese sample of mainly women, in treatment in a semi private facility in the capital city, the extent to which we can infer and generalize to the larger population from the findings is limited. However, the goal of qualitative research is not generalization, but rather understanding peoples' perspectives and experiences from their personal stories and comparing cases to discover patterns and themes (Patton, 2014).

Although the small sample would appear to be a limitation of the study, it is important to note that recruitment continued until saturation was reached (data replication/redundancy) i.e. similar findings were found in subsequent interviews indicating that the sample size was enough to fully capture the experience (Bowen, 2008). The representativeness of the sample

was another limitation because the proportion of male factor infertility was smaller than that reported globally, 25% and 40-50%, respectively (Kumar & Singh, 2015), because of the lack of male participants (n=3 of 20) and because the average age at marriage (average age minus average duration of marriage) for women in the sample (26.2) was older than the average age at marriage in Sudanese data [22.7] (United Nations, Department of Economic and Social Affairs, Population Division, 2015). These limitations would require duplication of interviews with more men and to ensure that the proportions of male to female factor infertility were reflective of true proportions.

The fact that this study was conducted in Sudan with mostly urban, educated individuals necessitates further replication in other locations with more diverse samples to enable a greater understanding of the need for fertility education and the acceptability and feasibility of the screening tool with those not represented in the current study. The interviewer was female which could have impacted social desirability bias and self-disclosure. Two of the men stated that they had engaged in premarital sex but none of the 17 female participants stated that they had. While it is possible that the woman might have been telling the truth, it is more likely that they did not want to admit to engaging in premarital sex given that Sudanese social norms strictly prohibit this behaviour for women. The exception was the one man who reported not engaging in premarital sex, but he was interviewed in the presence of his wife, therefore his self-disclosure might have been related to her presence.

Implications of Findings

The findings of this study can be used to inform implementation of the FertiSTAT in Sudan and the Middle East (and used to inform adaptation in other regions) and to endorse knowledge about optimal messaging in fertility education and other health promotion

endeavours. The data can also be used to make recommendations and suggestions for future research to fill gaps in knowledge.

Results of the current study lend support to the idea that culturally acceptable implementation of health promoting interventions like the FertiSTAT requires cultural sensitivity and tailoring of tools to the level of understanding and conservatism (modern v traditional) of not only the population but also of each individual. Cultural sensitivity can be achieved through a thorough understanding of the target audiences' culture which can be enhanced by garnering the support of people from the culture as was the case of the interviewer and research assistants being Sudanese and more aware of cultural factors (Kreuter et al., 2002). Results and interpretations can then be translated to print materials and seminars for fertility education (and other health education campaigns). The findings indicated that although taboo topics may not be acceptable to everyone, this does not mean that discussions about them should be avoided, rather a culturally and individually sensitive way to communicate about them should be sought. Participants suggested that sensitive topics should be addressed directly. Beyond this recommendation, the overreaching idea about tailoring information to the individual's level of religiosity or conservatism would suggest that sensitivity in provider version and appropriate titles to allow the provider to explain in the most appropriate way. For example talking about sex in a more conservative society like Sudan would be to address sex within the context of marriage and in the service of achieving reproductive goals. One such way would be through an integrated awareness campaign that includes information about sexual education, contraception and infertility within one comprehensive pamphlet or poster. Such a campaign can be integrated within existing healthcare and referral systems by being available at all levels of healthcare (e.g. primary health clinics, larger public hospitals and smaller private tertiary clinics). It can also be disseminated in schools and public places (e.g. markets, mosques). Specifically with the

flipchart, cultural tailoring can be achieved by making questions on the provider side of the flipchart that can help the provider gauge level of understanding, education and religiosity/conservatism, and tailor the materials/questions to the individual's specific level.

The need for several versions noted by the stakeholders (chapter 2) was confirmed from the data in the current study. Most notably that versions need to be specific to the target audience and setting, for example adolescent boys might not respond to pamphlets but will be interested in seminars, young girls might be more willing to engage with a women provider and that provider administered versions would allow for tailoring to individual needs. In addition to being an educational tool (like the flip chart) FertiSTAT can be used as a screen (like the checklist noted in chapter 2) and as an ice-breaker, a tool to start communication, as a starting point for discussion between patient and provider (e.g. flip chart, or checklist), as a way for people to talk about their fertility issues with each other (e.g. pamphlet) and as a way to introduce sex education and contraception within a culturally sensitive and acceptable context (e.g. poster).

Results of this study support reports in the literature about cultural sensitivity and cultural tailoring of health promotion tools for use in new contexts (Betsch et al., 2013; Kreuter et al., 2002). For example, the findings suggest that information which is compatible with worldviews is more readily acceptable and would lead to more efficient health education (as is the case with personalized information). That said, more research is need to confirm what the specific factors impacting behavioural change in different settings are (Betsch et al., 2013, Kreuter et al., 2002). Consideration of level of self-disclosure could be important and can be based on social desirability as evidenced from the data and the literature (Krumpal, 2013). Finally to enhance impact, fertility educational campaigns, in addition to providing information, should dispel common myths about the health behaviour or illness (Bunting and Boivin, 2008).

Future Research

Future research specific to implementation of FertiSTAT in the Middle East requires more focus groups in other countries (in the Middle East) and different samples (e.g. men, rural), formal translation and back translation of tools into Arabic. Small scale roll out of Arabic version of tools in samples of about 100 participants or more in several locations (e.g. urban and rural), followed by large scale country wide roll out. Simultaneously, the protocol for cultural adaptation of the FertiSTAT could be replicated in other regions (e.g. Asia) including identifying additional RFs, conducting stakeholder meetings and focus groups as well as translation and back translation of FertiSTAT into other languages and pilot and large-scale testing. Most importantly it will be integral to conduct follow up studies to measure impact after roll out of FertiSTAT on outcomes such as behavioural change in the lifestyle RFs (e.g. less smoking, more condom use) and change in help seeking practices (e.g. visiting the gynaecologist for menstrual dysfunction and signs of infection like STIs and BV), as well as changes in guidelines, policies and provider behaviour (e.g. testing for GTB in areas of high TB prevalence).

Conclusion

The Arabic saying ‘no embarrassment in knowledge’ echoed in the data captures the importance of health promotion and cultural sensitivity. Successfully implementing the FertiSTAT in Sudan and the Middle East would require an integration of cultural targeting and tailoring and the specific suggestions (format, setting, source and timing) to address perceived challenges to its effective use, namely the transition between modern and traditional societies, issues of self-disclosure and understanding of being at risk. These challenges highlighted the need for cultural tailoring that goes beyond culturally targeted materials that suit the entire culture to specific modifications to be compatible with each user’s worldview. It would appear that addressing the challenges identified through cultural

tailoring as suggested by the data and the literature would be the most effective way to achieve cultural sensitivity through congruence with worldviews. An understanding of the deep structure of Sudanese culture would ultimately enhance the feasibility and acceptability of using this tool in Sudan. Cultural adaption of FertiSTAT based on cultural tailoring will be congruent with the theoretical bases for the development of the tool that emphasize that personalized risk and guidance enhance impact of health messaging. Finally, lessons learned extend beyond implementation of FertiSTAT to fertility awareness and health promotion in general.

Chapter 5

General Discussion and the Adapted FertiSTAT

The overall aim of the studies presented in this thesis was to culturally adapt the Fertility Status Awareness Tool (FertiSTAT) for use in Sudan and other LMIC. These studies addressed the importance of fertility health in LMICs, specifically preventative care within a multidisciplinary global perspective. Adaptation processes encompassed an evaluation of the comprehensiveness of the items (Chapter 2, Study I and Chapter 3) and acceptability and feasibility including an understanding of the best methods for constructing and conveying materials (Chapter 2, Study II and Chapter 4). The results demonstrated that superimposing health messaging on new target populations would not be beneficial unless comprehensiveness, acceptability and feasibility were considered. The processes involved helped demonstrate an approach that can be utilized for the cultural adaptation of other health promotion materials. Through these processes several conceptual considerations emerged. For example, risk profiles of given populations should not be assumed to be universal, culture encompasses and influences much more than language and rituals and terminology used to describe fertility problems and the determinants of definitions are context specific. Additionally, several methodological considerations arose, namely, sampling and dearth of good quality primary studies. Knowledge attained from the activities was aggregated to produce the adapted versions of the FertiSTAT to be tested on Sudanese populations. This chapter presents these conceptual and methodological considerations as well as the adapted versions of the FertiSTAT.

Key Conceptual Considerations

Culture is Bigger than its Practices

Although, RFs could have a common underlying mechanism globally it would be mistaken to assume this universality necessarily implies similarity in the fertility RFs to which people are exposed globally or the method by which awareness of risk could be enhanced. There are many RFs such as age, reproductive disorders (e.g. endometriosis) and lifestyle (e.g. smoking) that affect women's fertility universally (e.g. see Appendix B; Schmidt, 2012; Stilley, 2012; Dechanet, 2011). However, it can be inferred from the results of studies carried out during this project that there may also be RFs for fertility problems that are not universal. These non-universal RFs can be due to cultural practices and rituals such as CSG and FGM/C, to infections more prevalent in certain regions such as GTB or to misuse of clinical practices such as D&C. Therefore, the implementation of successful fertility awareness needs to be inclusive of such divergent risk profiles.

The lack of universality in risk profiles can be in part due to the factors influencing behaviour of individual's within different societies and one such factor that became apparent from the studies was the influence of culture. Results of the current studies demonstrated that culture is the backdrop for risk, such that risks and risk exposure is influenced by culture, including norms about health protection behaviours (e.g. engaging in safe sex). Culture has been intensely explored in health promotion because racial and ethnic differences are associated with numerous health issues, such as rates of mortality and morbidity of various diseases, prevalence of risk behaviours and the determinants of health behaviours (e.g., U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2005). Therefore, to assume that culture could only influences fertility health through specific rights and rituals (e.g. FGM/C), would be naïve. Culture is a broad term and it will have many effects on behaviour but only some will have an effect on health and it is important to target those and not all rituals. For example, tribal facial marking would not

have an impact on reproductive health while genital cutting would. It is the change to the anatomy or physiology that will determine the mechanism or the impact of exposure rather than the ritual or practice per se. Given that culture can impact on exposure to risk in many ways (i.e., cultural rituals such as FGM/C, norms dictating health protecting behaviours, nature and exposure to risk behaviours) the multifaceted influences of culture need to be taken in to consideration in health promotion efforts.

Terminology and Decisions for the Selection of Risk Factors

The work presented in this thesis raised important considerations for what a fertility awareness tool could and should include as risks. The FertiSTAT was conceptualised as a multifactorial tool that could inform on risk status for reduced fertility. By reduced fertility was meant reduced ability to achieve a pregnancy. Women ticked each sign, symptom or preventable cause of fertility problems that applied to them and these individually and collectively informed on absence or presence of risk for reduced fertility for them. The tool minimised the number of indicators that needed to be included in the tool by only including indicators that did not have overlapping signs or symptoms. For example, menstrual irregularity puts women at risk of reduced fertility but including all causes of menstrual irregularity (e.g., strenuous exercise, weight loss) would reduce the predictive weight of each indicator, and make FertiSTAT cumbersome and unlikely to be useful in a practical context. Instead, the FertiSTAT included the signs of menstrual problems (short, long, irregular and absent periods) without naming each cause. It then provided guidance about when to seek medical help for these problems. Further, only indicators that women could detect were included because it was a self-administered tool. The work of adapting the FertiSTAT for LMIC called into question some decisions taken in the original development of FertiSTAT.

First, was the question of which outcome (and therefore related risk) should fertility awareness tools target. In the current studies the decision of which of the new RFs to include was initially based on whether there was enough meta-analytic and aggregated evidence to support its inclusion as an indicator for reduced pregnancy. FGM/C, HIV, BV and GTB were recommended because meta-analysis showed a significant association with infertility (12 months inability to achieve pregnancy). However in the case of CSG because results indicated significant association with stillbirth and neonatal death, it became apparent that the decision of whether CSG should or should not be included would ultimately depend on the perceived function of the tool. As noted, the developers of the FertiSTAT intended it to be used as a tool to raise awareness about fertility problems, from their perspective that included only problems achieving pregnancy (i.e., based on definition of infertility which only includes pregnancy, Bunting & Boivin, 2010). However, for LMIC the available evidence suggested the need for a more encompassing definition for fertility (Chapter 3, pp 50) that included the inability to achieve a live birth. This raises the question of how fertility problems in general should be defined in the context of fertility awareness. As discussed previously (Chapter 3, pp 50), there has been a range of definitions used for fertility problems including diverse outcomes (pregnancy, live birth), duration of exposure (number of months required before infertility is declared) and time span (that encompasses the period of infertility). This diversity is due to specific utility such as demographic, epidemiological or clinical purposes (Chapter 3, pp 50). New approaches to thinking about prevalence, for example the current duration, should also be evaluated (Polis, Cox, Tunçalp, McLain & Thoma, 2017; Slama et al., 2012). Current duration is used in cross-sectional examination of infertility prevalence estimates and is a way of measuring the current duration of unprotected intercourse (Polis et al., 2017; Slama et al., 2012).

In the primary studies it was noted that when the outcome was indicative of inability to achieve pregnancy the duration of exposure used tended to be 12 months, whereas for live births it was five or seven years, in line with discipline based definitions previously documented in the literature (Gurunath et al., 2011). In light of the diversity that already exists, and the plurality of purpose according to discipline, the aims of fertility awareness would be better served by having a broader definition of fertility problems in FertiSTAT for LMIC, including inability to achieve and sustain a pregnancy, or have a desired live birth.

A second issue arising from the work of this thesis is what fertility information women can be reasonably expected to have at the time of completing the FertiSTAT. The FertiSTAT is a tool to be used to raise awareness about risks for fertility problems so that people can make informed decisions about their health, or know when to seek timely medical advice. In the original FertiSTAT reproduction was not described and medical conditions impacting on fertility (e.g., cancer) were not included. It was assumed that women would know about such matters through their education or specialists. For example, regarding gestational RFs, it is safe to say that prenatal care in the UK would ensure that if a woman was at increased risk for a specific gestational problem she would be informed about this and the necessary action would be taken (e.g., screening for various conditions such as hypertension, see NICE Clinical guideline [CG62]). It cannot be assumed that the same would be true in LMIC where health care systems are overburdened, literacy rates are suboptimal and prenatal care may not be universal or its utility not well understood, thereby influencing its uptake. The same is true for medical conditions such as diabetes. In the UK these need not be included because the impact of such diseases on fertility would be communicated by the treating physician to the patient (e.g. effects of cancer treatment, see Royal College of Physicians, Royal College of Radiologists, Royal College of Obstetricians and Gynaecologists, 2007). Again, it cannot be assumed that the same would be true in

LMIC. Therefore, the inclusion of such gestational RFs and medical conditions would enhance fertility awareness in LMIC more than it would in the UK.

A third issue arising from this thesis is how to handle trade offs between comprehensiveness and implementation in designing fertility health awareness tools. Even though the inclusion in the adapted FertiSTAT of each of the RFs found to be associated with fertility problems (Chapter 3) would be in line with the broader understanding of fertility problems recommended, this comprehensive inclusion may not be practical. The inclusion of many individual RFs could dilute the predictive ability (validity) of the tool if their mechanism of action is already included in the FertiSTAT (e.g., including all causes of ‘absence of period’). Second, an exhaustive list could be time consuming and impractical to administer therefore reducing the likelihood of its use and increasing the cost-benefit ratio of the tool. An alternative approach might be to include categories of risk rather than all risks. For example, a question about presence or absence of medical conditions could include all medical conditions known to affect fertility (e.g., ‘Have you ever been diagnosed with any of these medical conditions: diabetes, cancer, kidney disease, sickle cell anaemia, thyroid disease, lupus’). This approach would be more comprehensive and culturally appropriate (i.e., assumption about base knowledge) than the original and yet as brief and cost effective. In light of all these considerations, it would be recommended that in LMIC the FertiSTAT could comprise the universal (original) FertiSTAT, the non-universal RFs, medical conditions and the RFs that have an impact on ability to achieve live births. The validity and predictive ability of the adapted FertiSTAT would need to be re-examined to determine if the addition of the new RFs diluted the predictive ability of the tool as a whole and to determine if each of the new RFs was an independent factor in prospective studies.

A final issue related to the inclusion of RFs that became apparent from the results was the fact that results aggregated across the literature indicated that the mechanism of action of

several RFs involved PID (HIV, BV, D&C) and TFI (FGM/C). These results diverged from the more general reproductive health literature emphasizing that in LMIC infections and PID are related almost exclusively to maternal infection (post-abortion and postpartum) and STIs (e.g. see, Ericksen & Brunette 1996; WHO, Infections, pregnancies, and infertility, 1987) rather than the more diverse causes shown in the reviews presented in the thesis. The findings suggest that perhaps the focus needs to be redirected to consider the impact of other prevalent diseases such as BV and preventing all RFs that can lead to infection. Clinical care should also be directed towards treating all infections (whatever their cause) before they ascend the reproductive tract and lead to more severe consequences such as PID and TFI.

Considerations about how to Address Fertility Awareness in LMIC

An important question that emerged from the current studies was how best to increase priority for fertility problems in national health plans in LMIC. It is likely that many actions would be needed, at a minimum would seem to be first to establish the need for fertility health awareness and second to emphasise that preventative measures are perhaps the most impactful in LMICs.

The importance of fertility health awareness comes from several arguments; the severe consequences, especially for women in LMIC and the ethical arguments which include equal rights to reproductive health and autonomy, LMIC not bearing the burden of over population, and prevention being the most cost effective for low resources settings where health care systems are overburdened (Ombelet, 2011). Globally, childlessness has severe negative psychosocial consequences and the burden is often borne by women in LMIC (Dyer, Abrahams, Mokoena, Lombard and van der Spuy, 2005; Greil, Slauson-Blevins & McQuillan, 2009; Riessman, 2000; Rouchou, 2013; Van Balen & Bos, 2010).

As noted previously prevention is often key to health care initiatives that aim at equity. Prevention through increasing knowledge is cost effective (ESHRE Task Force on Ethics and Law, 2009; Macaluso et al., 2010; Ombelet, 2011) and proven to be efficacious (Kok et al., 1997), especially when culturally sensitive (Kreuter et al., 2002; Resnicow et al., 1999). Moreover, it is well known that fertility knowledge is poor globally and in LMIC (Ali et al., 2011; Dyer, 2008), therefore, a tool like FertiSTAT that aims to enhance fertility knowledge would be beneficial and cost effective. In addition to increasing knowledge the FertiSTAT provides personalized feedback which according to HBM the experience of personal risk is a motivator for acceptance of health messaging (Noar et al., 2007; Parkes et al., 2008; Petty & Cacioppo, 1986).

Given the importance of fertility health awareness and the utilization of a preventative approach, raising awareness could be achieved by ensuring that tools developed and adapted are purposed for the context. LMIC contexts present unique instances of cultural diversity but are united by dearth of resources. Therefore, health promotion activities need to be purposed not only to be cost effective but to incorporate these cultural variances.

As previously noted, culture influences risk behaviours and the exposure to risk, additionally the current set of studies also demonstrated that health promotion can be more impactful if health messaging is compatible with worldview, congruent with the literature (Betsch et al., 2016). Therefore, communication of health messaging needs to be done in the most culturally sensitive manner to achieve maximum benefit (Betsch et al., 2016; Healey et al., 2017). This cultural sensitivity should incorporate both cultural targeting of new populations and cultural tailoring to be appropriate for each user (Kreuter et al., 2002; Kreuter & Skinner, 2000), as noted previously. This means that self-administered versions, as was the original format for FertiSTAT, may not be the most suitable format for all populations.

Another issue that emerged was whether raising awareness in LMIC should also emphasize the importance of personalized risk, as has been demonstrated in non-LMIC contexts (e.g. see Noar et al., 2007; Parkes et al., 2008; Petty & Cacioppo, 1986; Sohl & Moyer, 2007). Alternatively, it might be more cost-effective to have generic health messages that can reach a wider audience. However, results from current qualitative data (Chapter 4) would suggest that the need for personalized information was of utmost importance and could possibly influence the acceptance of the information. These results were based on information from a small sample and would therefore need to be replicated with a larger more diverse sample, to allow generalizations.

Additionally, a comprehensive fertility health awareness package would need to not only incorporate RFs relevant to a specific setting but should also include basic information about reproduction as well as de-mystifying commonly held myths. This is important because, not only is knowledge about fertility problems poor, knowledge about reproductive issues such as women's fertile period was low in studies in both developed and developing nations (Sydsjo, Selling, Nyström, Oscarsson & Kjellberg 2006; Byamugisha, Mirembe, Faxelid & Gemzell-Danielsson 2006). Bunting and Boivin (2008) found that participants were significantly more able to correctly identify the impact of RFs, than myths or healthy habits on fertility. This was corroborated by female participants in the pilot study who were unaware of basic physiology of intercourse (Chapter 4, pp 305).

All previously mentioned considerations suggest that health promotion should be tackled from a global and multidisciplinary approach that incorporates an understanding of how different cultures influence exposure to risk as well as acceptance of health promotion.

Global, multidisciplinary approach.

Global health transcends national boundaries and aims to provide health equity among nations in prevention and clinical care through a highly interdisciplinary and

multidisciplinary approach (Koplan et al., 2009). In that sense the objectives of the current project were motivated by the aim of globalizing the FertiSTAT and the combination of all activities and the fact that the project was conducted by and advised on by researchers from different countries enabled us to propose that a global perspective was used in the aims, objectives and activities of the project. Additionally, the project took a multidisciplinary approach to address the multifaceted issues involved. The development of the original FertiSTAT was rooted in health psychology as it focused on individual processes contributing to that person's health, and theories like the HBM (Bunting & Boivin, 2010). Through the process of adapting the tool, interest shifted to include how behaviours such as FGM or CSG and diseases such as HIV and GTB can affect health and because these are influenced for the most part by cultural norms, not only on an individual level like smoking, they are considered public health issues as they are population based. Additionally, the intervention is preventative and is therefore inherently a public health issue since public health is about preventing people from getting sick and promoting wellness by encouraging healthy behaviours (Koplan et al., 2009). In general, health promotion is an intersection between these two disciplines because it uses health psychology models about individual behaviour and sets it within the backdrop of societal based issues, so that the focus of intervention moves beyond the individual's behaviour towards societal and environmental issues (Kok, 2014). This global multidisciplinary perspective entailed tackling the adaptation process from several dimensions to shed light on the cultural underpinnings that could influence content and appropriate approach of health promotion activities.

Integrated life course approach to awareness.

There is a growing movement towards taking a holistic life course approach to women's health especially sexual, fertility and reproductive health (e.g. see Stephenson, 2011), recently advocated in WHO training framework (WHO, Development and Research

Training in Human Reproduction, 2017). The framework highlights the interlinked nature of sexual, fertility and reproductive health, as has been demonstrated in the present study. For example, STIs (sexual) have an impact on ability to become pregnant (fertility) and potentially ability to sustain or have a child (reproductive). It became apparent from the results of the studies in the thesis that this integrated holistic life course approach to sexual, fertility and reproductive health is the most optimal approach in Sudan and possibly other LMIC. Evidence from interviews (Chapter 4, pp. 305) indicated that some women felt comfortable discussing otherwise taboo topics such as sexuality in the context of fertility and reproduction and marriage. Furthermore, during the development of the flipchart (Chapter 2, pp. 31) it became apparent that basics of reproductive functioning such as intercourse would need to be explained due to lack of basic knowledge (as noted on pp. 350). An integration of all results in the thesis, led to the conclusion that women want an integrated sexual, fertility and reproductive health education.

Future adaptations of fertility awareness tools specifically and sexual, fertility and reproductive health messaging generally could benefit from such an integrated approach. This approach could provide several advantages, such as advocacy for and acceptance of potentially sensitive matters (e.g. sexuality, gender-based violence), practicality, cost-effectiveness and could benefit from researches in all relevant areas. Provision of such a topographic overview of the possible threats (and opportunities) in women's health would help prepare women for informed decisions about their health. Therefore, information within health messaging should complement awareness activities and be conveyed in a manner that capitalizes on the holistic way women view their reproductive lives. Carefully crafted educational content tailored to LMIC via effective methods (e.g., effective infographics, Otten, Cheng & Drewnowski, 2015) could depict the different aspects of sexual, fertility and

reproductive health issues faced at different times throughout the life course and how they interrelate with each other within and across time.

Key methodological Issues

The methodology used in the project was relatively strong because a mixed methods approach was used, such that quantitative evidence including survey and systematic reviews was combined with qualitative evidence from stakeholder meetings and patient interviews. A mixed methods approach is one that combines qualitative and quantitative methodologies to provide a more elaborate and deeper understanding of a phenomenon (Johnson, Onwuegbuzie & Turner, 2007). Therefore, the agreement or convergence of results of two methods validates the results as occurring due to real effects and not as a result of methodological characteristics (Bouchard, 1976), as was the case in the current studies. However, several limitations existed.

Sampling Issues

The main limitation of the project was recruitment in the survey of fertility doctors in LMIC (chapter 2). Although 150 potential participants were approached through email invitation, only 41 (27.3%) participated. Additionally, not all participants answered all questions in the survey, therefore the response rate for questions varied. The low survey response rate, could affect results because it is unknown whether responders were representative of the cohort of fertility doctors from LMIC. This is important because samples need to be representative of the populations to which generalizations will be made (Heiman, 1999). It could be that only doctors with an interest in fertility awareness completed the survey or only those with enough time and they could have a different perspective from doctors not involved in fertility or being busier. However, the data (Chapter

2, pp 23-24) indicated that the doctors varied in terms of private and public sector practice and with regards to number of patients seen per week, indicating that while some were engaged in both private and public practice and saw upwards of 20 patients per day, others were only in private practice and saw about five patients per day. More importantly, the low response rate is not unique to this sample, as it is known that when surveys are received without prior notice, as was the case in our study, the response rate is approximately 20% (Kelly, Clark, Brown & Sitzia, 2003). It is important to note that information from the survey was not relied on solely in the identification of RFs. Rather, the survey information was used to confirm the selection of RFs identified through literature search and expert consultations using considerations cited in the literature (Ezzati et al., 2002; Chapter 2, World Health Report, WHO, 2002). Therefore, the limitations of the survey may have little impact on the results of the project as a whole.

Sampling issues were limitations of the qualitative interviews as well (Chapter 4). These interviews were conducted to ascertain acceptability and feasibility of the adapted versions by potential users but were only conducted with Sudanese couples attending at an infertility clinic. This sample might not have been representative of typical potential users in that it was mainly urban, educated women with fertility problems that were for the most part due to female factor infertility. Interviews with proven fertile and untreated infertile couples might have led to different conclusions about the acceptability and feasibility of the adapted FertiSTAT. For example, couples who have children and have never faced fertility problems may not see the importance of raising awareness regarding fertility health and infertile couples who are not in treatment may be in denial about their problems and take offence.

Primary Studies in Systematic Review

The main limitations of the systematic reviews related primarily to the lack of availability of good quality primary studies. The lack of good quality primary studies testing the association of the identified RFs with fertility problems, limited the generalizability of the results of the systematic reviews. Available primary studies were all observational, limiting conclusions about causality (Mann, 2003), and for the most part had methodological weaknesses especially regarding operational definitions of outcomes and clinical sampling.

Adapted versions of the FertiSTAT

Cultural adaption of the FertiSTAT lead to the development of two tools, a flipchart and a provider checklist (see Appendices T and U). These tools were based on an integration of all materials, knowledge and experiences garnered through the activities described in the thesis. Both tools contained questions about age, time trying, reproductive medical history (e.g. endometriosis, PID and BV), lifestyle risk factors (e.g. Smoking) that would also include practices and rituals (e.g. FGM/C), and medical history (communicable e.g. GTB, HIV and non-communicable diseases e.g. diabetes). The one page checklist consisted of two sections (women and men) and the flipchart consisted of 34 pages each for the provider and the user. The provider side included instructions to assess the user's particular level of education and understanding to convey information in the most appropriate manner. Additionally, these instructions included an assessment of religiosity and modern-traditional values for sensitive topics such as sex, alcohol and drug.

The adapted tools were culturally targeted at Sudanese populations by including risk factors (RFs) pertinent to Sudan, namely, FGM/C, CSG, BV, GTB and HIV and by being linguistically and graphically culturally sensitive. Furthermore, an understanding of the deep structure of Sudanese culture enhanced the adaptation of these tools for use in Sudan, as evidenced by the need to allow for cultural tailoring of communication to suit the cultural

attributes of each user. In addition to the adapted tools, the specific studies within the thesis can be used as a protocol for adaptation of the FertiSTAT to new contexts. The original FertiSTAT provided women with a personalized assessment of their risk of fertility problems (Bunting & Boivin, 2010) and the adapted versions went further by being culturally targeted at a sub-population of the LMIC, Arab, African and Muslim culture (i.e. Sudanese population) and by affording the space necessary to provide cultural tailoring to the needs of each individual within that subculture.

Future Research

Results of the project lead to the conclusion that there is a need for more primary studies to be conducted to test associations of exposure to non-universal RFs and fertility problems. These studies should adhere to best practice in research methodology including using operational definitions of fertility problems such as those in the newly published ICMART-WHO glossary of terminology relevant to medically assisted reproduction (Zegers-Hochschild et al., 2017). Where possible RCTs, or stratified RCTs should be carried out to enable assessment of cause and effect relationships between the non-universal RFs and fertility problems. Once more primary studies of high quality are conducted, systematic reviews should be updated to definitively ascertain the impact of exposure to non-universal RFs on fertility health.

Future research specifically regarding fertility awareness and the adapted FertiSTAT tools should include several issues. First, updating the personalized guidance, to incorporate the new RFs, using the same methodology applied in the development, for example Delphi rounds with fertility health experts (Bunting & Boivin, 2010). Second, testing the adapted versions on more diverse populations within the Sudan (e.g. rural, fertile and/or adolescents). Third, testing the new FertiSTAT tools, to determine the predictive ability of the newly

incorporated RFs and whether they are independent and to determine if the flipchart and checklist modalities are the best methods to convey the information. Fourth, adapting the materials to other LMICs and testing new materials in those populations. Finally, further research on fertility awareness programmes in LMIC should not only focus on fertility problems, but a wider perspective more inclusive of all aspects of fertility health such as reproductive health, family planning, prevention of STIs and HIV, should be applied.

Conclusion

The principal lesson learnt through these studies was that it was possible to adapt the FertiSTAT but like other health education tools it required cultural adaptation because it could not be assumed that a global set of RFs would be able to capture all issues unique (and health critical) within various specific environments. Risk profiles of nations, regions and globally need exploration and should not be assumed to be universally analogous. Therefore, evaluation of the content of health messages to be culturally accurate by incorporating risk profiles of target populations is necessary. Furthermore, cultural adaptation needs to go beyond cultural targeting that includes translations and graphics to cultural tailoring of materials to suit individual needs. Finally, investigating the most suitable way to convey health messaging, including the most sensitive wording, format, setting and source need to be investigated within the target populations and using different methodologies (e.g. survey, interviews and stakeholder meetings).

Diversity necessitates examination of the influence of global diversity on risk profiles, appropriate language of communication, target audiences and settings of implementation, and ultimately the need to engage in a process for the adaptation of fertility awareness tools. Lessons learnt could be applied specifically to fertility health and generally to health

promotion to enhance global health equity, to alleviate suffering and to help ease the burden of disease for individuals, communities, healthcare systems and providers globally.

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Appendices

Appendix A: Fertility Awareness Status Tool (FertiSTAT)

Do you know about your fertility?

If you're planning to have children now or in the future you need to start taking care of your body right now. Calculate your FertiSTAT score and find out what you can do for your fertility. You can calculate your FertiSTAT score whether you are currently trying to get pregnant or not. If you are not trying to get pregnant, choose your age group and consider yourself trying for under 6 months in the 'About trying' section.

1. Tick all the coloured boxes that apply to you

About trying to get pregnant:

- B** 34 years of age or younger and trying for 0 – 12 months
- B** Over 34 years of age and trying for 0 – 6 months
- R** Over 34 years of age and trying for 6 or more months
- R** Any age and trying for more than 12 months

Your reproductive history:

- O** I suffer from severe period pains
- O** I have had pelvic surgery
- O** My menstrual cycle is unpredictable. My period often comes more than 5 days earlier or later than expected (when I am not using contraceptives)

- O** My menstrual cycle lasts less than 21 days (when I am not using contraceptives)
- O** My menstrual cycle lasts more than 35 days (when I am not using contraceptives)
- O** I suffer from endometriosis
- O** I have had pelvic inflammatory disease (PID)
- R** I do not have a period (when I am not using contraceptives)

Your lifestyle:

- Y** I have unprotected sex with multiple partners
- Y** I smoke regularly (more than 10 cigarettes per day)
- Y** I cannot cope with the stress I am currently experiencing

- Y** I drink more than 14 units of alcohol per week (1 unit = a small glass of wine, ½ pint of beer, a single measure of a spirit)
- Y** I drink more than 7 units of caffeine per day (1 unit = a cup of coffee, ½ unit = a cup of tea or a can of soft drink such as cola)
- Y** I smoke marijuana frequently (more than four times a week)
- O** I have had a sexually transmitted infection
- O** I am more than 13 kilos (28 pounds/2 stone) overweight
- R** I have used class A drugs in the past (e.g., heroin, cocaine, ecstasy)
- R** I am currently taking anabolic steroids (for non-medical uses)

To consider your male partner's fertility status complete the lifestyle section (except weight) for him and follow the guidance for these factors. If your partner has (or has had) undescended testicles **R** or mumps after puberty **R** then he needs to go and see his doctor for further investigation about his situation when you start trying to get pregnant with him.

2. What does your FertiSTAT score mean?

In the meters below circle the number that equals the boxes you have ticked for each colour category and find out what action you need to take*. If your answer falls into more than one category please read all the advice.



*The more ticks you have within each colour category the greater the need to take action if you are trying to get pregnant.

Appendix B: Summary of Findings from Reviews on the Impact of Original FertiSTAT Risk Factors on Fertility

Risk factor	Summary findings	Type of review	Source
Age, lifestyle and reproductive			
Age	Increasing parental age is a risk factor for reduced fertility.	Narrative Review	Schmidt, 2012
Age	Birth rate starts to decrease when a woman reaches 35 years old. Young women conceive sooner than older women. Infertility increases as the age of the female increase.	Narrative Review	Liu, 2011
Appendectomy	No statistical association between appendectomy and infertility	Systemic Review and meta-analysis of RCTs	Elraiyah, 2014
Pelvic surgery	Adhesions are a common complication of gynaecological surgeries. Adhesions affect the interaction between the fallopian tube and ovaries consequently infertility can occur.	Narrative review	Hirschelmann, 2012
Chlamydia	Inflammatory tissue destruction in response to infection leads to the development of tubal infertility and ectopic pregnancy	Narrative Review	Carey 2010
Endometriosis	Dysfunction of pituitary-ovarian axis altering the feedback pathways, folliculogenesis, lower levels of estrogen and progesteron, altered luteal function and the fact that they ovulate fewer oocytes are all accounted for infertility in women with endometritis	Narrative review	Stilley, 2012
Lifestyle	Fertility is decreases by being overweight and underweight. Folic acid and Vitamin B have been linked to infertility and spontaneous abortions. High alcohol consumption can affect estrogen and progesteron levels leading to anovulation, luteal phase dysfunction and impaired implantation. Consumption of caffeine in moderation has no effect on fertility however some evidence suggest that prolongs time to conception. Smoking adversely effects fertility and pregnancy outcomes. Recreational drugs are associated with decrease fertility, some prescription medications such as anti-hypertensives can affect the female reproduction on different levels. Stress can supress the reproductive functions such as causing hypothalamic amenorrhea. Environmental pollutant can cause a negative effect on fertility. Evidence of oxidative stress has been found in women with PCOS, unexplained infertility and endometriosis.	Narrative Review (in some cases review of reviews e.g. in smoking several systematic reviews and meta-analyses are reviewed here)	Anderson, 2010
Lifestyle	Increasing age of a women increases infertility and time to pregnancy.	Narrative review	Sharma 2013

Risk factor	Summary findings	Type of review	Source
	<p>Consuming more vitamins & proteins and less carbs & trans fats are recommended to preserve fertility.</p> <p>Body weight has significant effect on infertility. Obesity increases the risk of miscarriages however being underweight is associated with ovarian dysfunction and infertility.</p> <p>Vigorous exercise was found to have a negative effect on female reproduction by causing hypothalamic dysfunction and therefore menstrual abnormalities.</p> <p>Physical stress can prolong the time to conceive, however psychological stress is more prominent among women attending the infertility treatment.</p> <p>Smoking decrease the ovarian function and ovarian reserve.</p> <p>Marijuana use increases the risk of primary infertility. Prescription medications such as anti-psychotics, anti-hypertensives and chemotherapy.</p> <p>The amount of alcohol and caffeine consumed significantly affects the fertility of women.</p> <p>Exposure to heavy metals such as lead is reported to alter hypothalamic-pituitary axis and overall fertility.</p>		
Obesity	Obesity increases the risk of anovulatory infertility because of hyperandrogensim through granulosa cell apoptosis, peripheral conversion of androgens to estrogen leading to an increase negative feedback of gonadotropins and adverse effect on theca and granulosa because of increased leptin. PCOS is closely related to obesity but whether obesity causes PCOS is still undetermined	Narrative review of retrospective studies	Metwally, 2007
Smoking	Smoking effects fertility by impairing folliculogenesis and steroidogenesis. The effect of cigarette toxins depends on the amount and duration of exposure.	Systemic review	Dechanet, 2011
Smoking	There is a significant increased risk of infertility in women who smoked. Active cigarette smoking is associated with infertility. In some studies, smoking more than 20 cigarettes per day seem to effect fertility.	Systemic Review and metanalysis of observational studies (case-control and cohort)	Augood, 1998
STIs	<p>Adhesions cause by PID effects the tubes more than the uterus. Most of these pathogens lead to tubal infertility through an ascending infection.</p> <p>M. genitalium cause salphingitis-PID which may account for infertility. Ascending infection from N. gonorrhoea, C. trachomatis, Gradenella vaginalis lead to tubal factor sterility. Genital amoebiasis can cause damage to the female reproductive system and sterility.. HIV adversely effects fertility but it is not understood whether the impact is from the virus or concomitant genital infection or the effect of treatment.</p>	Narrative review	Pellati, 2007
Medical conditions			

Risk factor	Summary findings	Type of review	Source
Asthma	The inflammatory immune response caused by asthma was found in the uterus and tubes of asthmatic women. It causes chronic peripheral inflammation that alters the whole body's inflammatory response. The link that metabolic response is a risk factor for asthma implies that PCOS is related to asthma as well. An imbalance of the adaptive immune system is associated with infertility.	Narrative review	Gade, 2014
Cancer	Cancer-directed therapies reduces the ovarian reserve. Many chemotherapy agents have been linked to ovarian failure and radiation can lead to damage to the reproductive organs.	Narrative review	Levine, 2015
Chemotherapy	Female infertility due to ovarian damage from chemotherapy is an inevitable consequence. Chemotherapy causes irreversible and progressive damage to the ovaries and germ cells. Radiotherapy impairs the development of the uterus in young women and increases the risk for ovarian failure.	Narrative review	Lmai, 2007
Celiac Disease	Celiac Disease is relevant in women with unexplained infertility. Delayed menarche and amenorrhoea are also symptoms of Celiac Disease. Secondary amenorrhoea and spontaneous abortions were common in women with Celiac Disease. This can be attribute to deficiency of trace elements and vitamins due to malabsorption associated with Celiac Disease, this are responsible for a healthy reproductive life such as abnormal ovarian axis, p	Narrative review	Ozgor, 2010
Diabetes	Type I diabetes impacts the reproduction in many ways. Women with Type I diabetes have hypogonadotropic hypogonadism which causes amenorrhoea. Disturbed insulin secretion whether high or low impacts ovarian development and function and can aid in the development of PCOS. Studies on young adult women show preserved ovulation however they found fewer pregnancies and live births. Hyperandrogenism has also been associated with diabetes,	Systemic review	Codner, 2012
Lupus	POF in lupus patients can be due to autoimmunity or drug related. Patients with SLE can suffer from menstrual disturbances which has been associated with anti-corpus luteum antibodies which suggests autoimmunity as well	Narrative review	Hickman, 2011
Sickle cell disease	Women with sickle cell disease have lower number of pregnancies and delayed menarche.	Narrative review	Smith-Whitley, 2014
Thyroid diseases	Both hypothyroidism and hyperthyroidism are linked to menstrual abnormalities ranging from amenorrhoea to menorrhagia and subsequently leading to lower pregnancy rate and infertility.	Narrative review	Poppe, 2007

Note. STIs = sexually transmitted infections; PID = pelvic inflammatory disease; PCOS = polycystic ovarian syndrome

Appendix C: Approval for an Online International Survey of Fertility Doctors

The School of Psychology Ethics Committee has considered your postgraduate project proposal: Adaptation of the FertiSTAT to low human development index countries (EC.15.04.14.4130G).

The project has been approved.

Please note that if any changes are made to the above project then you must notify the Ethics Committee.

Best wishes,

Natalie

School of Psychology Research Ethics Committee
Cardiff University
Tower Building
70 Park Place
Cardiff
CF10 3AT

Approval for an amendment to administer paper copies of the survey in Sudan

The School of Psychology Ethics Committee has considered the amendment to your postgraduate project: Adaptation of the FertiSTAT to low human development index countries (EC.15.04.14.4130GA).

The amendment has been approved.

Please note that if any further changes are made to the above project then you must notify the Ethics Committee.

Best wishes,

Natalie
School of Psychology Research Ethics Committee
Cardiff University
Tower Building
70 Park Place
Cardiff
CF10 3AT

Appendix D: Fertility Doctors Survey**A. Recruitment Email:**

Dear Sir or Madam,

Your expert input is kindly requested in the Global FertiSTAT project.

The **World Health Organization** and **Cardiff University** are jointly funding the project. The primary investigator for this project is Professor Jacky Boivin (Boivin@cardiff.ac.uk) with the collaboration of Sheryl van der Poel (WHO, Geneva) and Ian Cooke (Professor Emeritus, Sheffield University) and the assistance of Ms Rasha Bayoumi (under the supervision of Prof Boivin).

The Fertility Status Awareness Tool (FertiSTAT) is a self-administered, 22-item tool developed in the UK to raise awareness of risk factors affecting female fertility (Bunting and Boivin, 2010). The aim of the Global FertiSTAT project is to adapt this tool for use worldwide. We hope that the Global FertiSTAT can be used by doctors and health care workers to help women get personalised fertility instructions, to protect their future fertility and to seek timely medical advice.

Your professional opinion on the risk factors affecting female fertility is kindly requested in the present survey to generate risk factors that could be incorporated in the Global FertiSTAT.

You will be asked to complete a short 9-item online survey that will only take about 10 minutes, and all the information provided will be anonymous. You will not be asked to provide your name with the answers and only the research team will have access to anonymous data. If you wish to participate, please click the link below:

https://cardiffunipsych.eu.qualtrics.com/SE/?SID=SV_5ARTZhwTlhLiYqp

If you would like more information about the project or have any questions please do not hesitate to contact Professor Jacky Boivin or Rasha Bayoumi at cardiffertilitystudies@cardiff.ac.uk

Thank you for your time and consideration

Best regards

Rasha Bayoumi

PhD Student

School of Psychology

Cardiff University

Tower Building

Park Place

Cardiff

CF10 3AT

B. Online Survey:**Risk Factors Affecting Female Fertility**

The aim of the Global FertiSTAT project is to adapt the Fertility Status Awareness Tool (FertiSTAT), which was developed and tested in the UK and is designed to help women safeguard their fertility and increase their chances of potentially achieving a pregnancy. It is anticipated that the adapted FertiSTAT can be utilized as both a patient and provider screening tool worldwide.

The World Health Organization and Cardiff University are jointly funding and providing technical support for the project. The primary investigator for this project is Professor Jacky Boivin (Boivin@cardiff.ac.uk) with the collaboration of Sheryl van der Poel (WHO, Geneva) and Ian Cooke (Professor Emeritus, Sheffield University) and the assistance of Ms Rasha Bayoumi (under the supervision of Prof Boivin).

In this study you will be asked to provide your expert opinion on risk factors for infertility in a short online survey (10-15 minutes). This is a voluntary study and you can stop participation by clicking out of the survey at any time. The information you provide is anonymous and there is no way of linking your name and your responses. The anonymous responses will be retained indefinitely for analysis.

If you understand the statement above and freely consent to participate in this study, please tick YES and continue by clicking 'Next' below. If you do not want to complete the survey please close this window now

YES

This project has received ethical approval from the University of Cardiff, School of Psychology Research Ethics Committee.

At the end of the survey you will be provided with additional information about the project. Please feel free to discuss questions or concerns with Professor Jacky Boivin (Boivin@cardiff.ac.uk).

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Section 1

Original Risk Factors

The list of risk factors associated with reduced fertility in the original FertiSTAT related to:

- Age
- Time trying to conceive
- Sexual history
- Menstrual cycle length
- Sexually transmitted infections
- Pelvic surgery
- Pelvic inflammatory disease
- Endometriosis
- Alcohol use
- Tobacco use
- Class A drug use
- Caffeine use
- Steroid use
- Stress level
- Obesity

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Section 2

Medical Conditions

Please indicate whether you think any of the following medical conditions or their treatment (e.g., medication, surgery) reduce fertility and should be included in the revised FertiSTAT.

	Should the condition be included in Global FertiSTAT?	
	YES	NO
Diabetes	<input type="radio"/>	<input type="radio"/>
Kidney disease	<input type="radio"/>	<input type="radio"/>
SLE (lupus)	<input type="radio"/>	<input type="radio"/>
Sickle cell anemia	<input type="radio"/>	<input type="radio"/>
Cancer	<input type="radio"/>	<input type="radio"/>

Please list below any other medical condition(s) that you think affect fertility and should be considered in the Global FertiSTAT?

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Section 3

New Risk Factors

The following is a list of potential new risk factors that could be included in the Global FertiSTAT. Please indicate if you think any of these factors should be included and state why in the column ‘reason/justification’.

You can go back to see the original FertiSTAT items at any time by clicking the <<Back>> button.

Please spell out any abbreviations you use

If you don't have a reason please leave blank	Should be included in Global FertiSTAT		Reason/justification for inclusion
	YES	NO	Answer
Post-abortion Infection	<input type="radio"/>	<input type="radio"/>	
Postpartum Infection	<input type="radio"/>	<input type="radio"/>	
HIV	<input type="radio"/>	<input type="radio"/>	
Genital Tuberculosis	<input type="radio"/>	<input type="radio"/>	
Bacterial Vaginosis	<input type="radio"/>	<input type="radio"/>	
Repeated D&C	<input type="radio"/>	<input type="radio"/>	
Cervical Electrocautery	<input type="radio"/>	<input type="radio"/>	
Female Genital Circumcision	<input type="radio"/>	<input type="radio"/>	
Consanguinity (couple blood relatives)	<input type="radio"/>	<input type="radio"/>	
Waterpipe smoking	<input type="radio"/>	<input type="radio"/>	

Other Risk Factors

Please state other risk factors you think reduce fertility and that could be included in the revised FertiSTAT:

Please include as many factors as you wish. For the present study it is sufficient to state your clinical or professional experience independent of actual evidence for or against these factors. There are no right or wrong answers.

	New Risk Factor	Reason/justification for inclusion	Particular level (critical threshold)
Other (1)			
Other (2)			
Other (3)			
Other (4)			
Other (5)			

Please provide any other comments or feedback about the Global FertiSTAT project or this survey?

(PAGE BREAK)

Medical professional background and practice

1. In which country do you practice?

2. What is your specialization? Please check all that apply:

- Obstetrics and Gynaecology
- Reproductive Medicine Sub-speciality
- Reproductive Endocrinology and Infertility (REI)
- Other Training in infertility, please state: _____
- Other Certification in infertility, please state: _____
- Other medical training, please state: _____

3. How many years have you been a medical doctor?

4. How many years have you been a fertility doctor?

5. Where do your fertility consultations take place? Check all that apply

- Primary Health Care
- Public hospital
- Private hospital
- Private clinic
- Other, please state: _____

6. How many fertility patients do you see per week? By fertility patients we mean patients having trouble conceiving.

7. What percentage of your practice is spent with fertility patients?

SUBMIT

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Further Information about the Global FertiSTAT project

Adaptation of the FertiSTAT to Global Settings

Thank you for your time in completing this survey

The Fertility Status Awareness Tool (FertiSTAT) is a self-administered, multi-factorial tool that can enable women to get personalized fertility guidance (Bunting and Boivin, 2010). The aim of the Global FertiSTAT project is to adapt this tool to raise awareness of fertility risk factors in settings worldwide. The World Health Organization and Cardiff University are jointly funding the project.

The purpose of the present survey was to generate new risk factors from diverse settings to ensure that the Global FertiSTAT is suitable for a worldwide audience. Following the completion of the survey, a systematic review of the newly identified risk factors will be conducted. Risk factors that can be empirically supported will then be included in a format of the FertiSTAT that can be used globally. The suitability and comprehensiveness of the new FertiSTAT items will be evaluated in a Sudanese population. The desired outcome of the project is a prototype of the Global FertiSTAT and a protocol for the adaptation process that could be used in other settings where there is an expressed need or desire to use this simple yet effective tool.

As a patient focused tool it can help empower women because it gives them the personalized knowledge about how to change their lifestyle and seek medical advice to protect their fertility potential. As a provider focused tool it could be an initial step that bridges gaps that enable people to seek timely medical advice when required. The FertiSTAT can be a quick and cheap way of assessing risk without any medical tests or interventions which may be unavailable or unaffordable in settings where access to fertility assessment is limited or non-existent. It can be administered by non-medical personnel, thus providing low resource clinics with a means of assessing those who may need to be referred for further investigation. Finally, the severe negative psychological and social consequences of childlessness (e.g., stigma, isolation, marital instability and divorce) are very serious and any tool that can help couples prevent infertility or help overcome it would be helpful to communities (Van Balen and Bos, 2010).

Please note that the data provided through this survey will be held anonymously.

If you have any further questions about this research or you would like an update of the activities of the Global FertiSTAT then please contact the principal investigators:

Professor Jacky Boivin
Supervisor
School of Psychology
Cardiff University
Tower Building
Park Place
Cardiff
CF10 3AT

Rasha Bayoumi
PhD Student
School of Psychology
Cardiff University
Tower Building
Park Place
Cardiff
CF10 3AT
cardiffertilitystudies@cardiff.ac.uk

Professor Jacky Boivin is interested in the psychosocial aspects of reproductive health. She has conducted many studies in this area on issues such as the link between stress and fertility, differences between men and women in emotional reactions to fertility problems, whether counselling helps people cope with fertility problems, how children conceived with fertility treatment develop, and much more. This research has been carried out with the help of women from many countries worldwide. You can see some of the published reports of this work on Professor Boivin's website at the School of Psychology, Cardiff University;

<http://www.cardiff.ac.uk/psvch/home/boivin/indexmain.html>

If you wish to make a complaint, please contact:

Secretary of the Ethics Committee
School of Psychology
Cardiff University
Tower Building
Park Place
Cardiff
CF10 3AT
Tel: (+44)29 2087 0360
Email: psychethics@cardiff.ac.uk

Appendix E: Steps and MeSH search terms used for search

Step 1:

MeSH terms for fertility combined using 'OR':

1. Fertility
2. Infertility
3. Female Fertility
4. Female Infertility

Step 2:

MeSH terms for RF combined using 'OR'

Step 3:

Combine step 1 and 2 using 'AND'

Step 4:

Removed duplicates

Appendix F: Exclusion criteria used for all risk factors (RFs)

Studies were excluded if:

1. The study reported on non-human subjects only
2. The study reported on male data only
3. RF was measured but there was no fertility related outcome
4. RF and fertility related outcome measured but the fertility outcome reported was not of interest (e.g. not specific about the duration of the infertility)
5. Both RF and fertility related outcome measured but the association between them not tested or reported
6. RF reported not of interest (e.g. acronym stands for something else)
7. Only secondary data analysis
8. Qualitative data only (including comments or letters)
9. Related publication
10. Duplicate record

Appendix G: MeSH terms used in the updated search

Amenorrhea

Time to pregnancy

Reduced pregnancy rate

Menstrual irregularities

Tubal occlusion/blockage

Reduced live birth rate

Childlessness

Childless

Time to first birth

Appendix H: Data Extraction and Critical Appraisal Form

Section 1. Data Extraction

Study ref: First author/ year/study number			
Data extracted by:			
Date:			
Aim/hypothesis (explanatory or descriptive study)			
Study design	Case-control / cohort study / RCT / Cross-sectional /		
	Multi-centre / Single-centre		
Demographics	Country		
	Ethnicity		
	Socio-economic		
	Other		
	Study period		
Study population			
Sample size	Risk factor (RF)	No Risk factor (No-RF)	Total:
RF definition (exposed)	RF: ➤ POITIVE ➤ NEGATIVE		
	Self-report OR Medical Test (specify which test)		
	Selection	Convenient sample / Random sample / Eligible: Invited:	
	In/exclusion criteria		
Control definition (non-exposed)	Selection	Self-report / other	
	RF status verified		
	In/exclusion criteria		
Comparability case- control (exposed/non-exposed)	Matching		

	Confounders	
Cohort specifics (if applicable)	Duration of follow up	
	Intervention/Comparison	
	Other	
Confounding Factors	Age	
	Age at marriage	
	Duration trying to conceive	
	Trying to conceive	Yes / no / not reported
	Use of Contraceptives	
	SES	
	Rural vs. Urban living	
	Stage of the disease	
	State of health (including weight)	
	Education	
	Marital status (never married, cohabiting, married)	
	Parity	
	Other (FertiSTAT indicators) Cross out all that apply	Over 34 years, trying for more than 12 months, severe period pain, pelvic surgery, irregular/short/long menstrual cycle, endometriosis, PID, no period, unprotected sex with multiple partners, smoking, can't cope with stress, alcohol, caffeine, marijuana, STI, overweight, class A drug, anabolic steroids
Other (not FertiSTAT indicators)		
Fertility Outcome measures used: (incl cut-off and Number of items)	Risk of infertility	
	Time to pregnancy	
	Reduced conception rate/ Pregnancy rate	
	Menstrual irregularities/Hormonal levels	

	Specific diagnosis (e.g. POI)				
	Childlessness (specify time period)				
	Time to first birth				
Outcome (infertility) (report test statistic, P value, odds ratio, confidence interval, CI)	Measure	RF	No-RF	Statistic	CI or p-value
	Risk of infertility				
	Time to pregnancy				
	Pregnancy rate				
	Menstrual irregularities				
	Hormonal levels				
	Specific diagnosis				
Subgroup analysis done? (what? Sign or N.S.)					
Results: Is RF related to infertility? (correlations / interrelationships between variables)					
Other significant differences between the groups?					
Context specification?					
Authors conclusions					
Data extractor comments (statement on quality which will be informed by data extraction and critical appraisal)					

Section 2. Quality Assessment**Ottawa Quality assessment scale observational studies**

Indicate two ** one * or leave blank

SELECTION		
1. RF adequately assessed? <ol style="list-style-type: none"> Independent validation of RF (medical testing or reference to primary record source such as medical/hospital records) * Self-report No description 		
2. Representativeness of the RF Cohort <ol style="list-style-type: none"> Representativeness of exposed individuals in the community * Not satisfying 		
3. Selection of controls/non-exposed cohort <ol style="list-style-type: none"> Adequate control selection for research question (community based / hospital based) * Same community as cases however derived from specialized population. No description 		
4. Definition of controls/non-exposed cohort <ol style="list-style-type: none"> RF is excluded properly in the control population * Not stated 		
COMPARABILITY		
5. Comparability of cases and controls (exposed/non-exposed) matching or adjusted in analysis (max 2 stars) <ol style="list-style-type: none"> Study controls for {most important confounder for this RF} (*) Study controls for other confounds (*) 		
EXPOSURE/PREDICTOR/OUTCOME		
6. Were confounds (such as age) adequately assessed? <ol style="list-style-type: none"> Obtained from medical/demographic records * Obtained from interview blind to case/control * Obtained from interview NOT blind to case/control Self-report No description 		
7. Was the same method used for both cases and controls? <ol style="list-style-type: none"> Yes * No No description 		
8. Outcome (such as Risk of infertility, Time to pregnancy, Reduced conception rate, Menstrual irregularities, Specific diagnosis) not present at the start of the study <ol style="list-style-type: none"> No * 		

<p>b. Yes</p> <p>9. Were outcomes adequately assessed?</p> <p>a. Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.) *</p> <p>b. Self-report (i.e. no reference to original medical records to confirm the outcome)</p> <p>c. No description.</p>		
<p>10. None response rate or loss to follow-up</p> <p>a. Same rate for both groups and <20% low to follow up *</p> <p>b. Non respondents described and unlikely to introduce bias</p> <p>c. Rate different and no designation OR not stated</p> <p>d. No description</p>		

Appendix I: Calculation of odds ratios from raw data in case-control studies for use in meta-analysis

Basic premise that allows the calculation (Kirkwood & Sterne, 2003, Chapter 16, pp160): the odds of having the disease in the exposed compared to non-exposed groups (odds ratio of exposure) is equal to the odds of exposure in the disease compared to health groups (odds ratio of disease).

Steps required to calculate odds ratios from raw data:

1. Understanding the 4 x 4 table required to calculate the odds ratio (OR)

	Exposed	Non-exposed	Total
Disease	a	b	a+b
Healthy	c	d	c+d
Total	a+c	b+d	

2. An OR is calculated as follows:

$$\text{OR} = \frac{\text{odds in exposed group}}{\text{odds in non-exposed group}} = \frac{a/b}{c/d} = \frac{a \times d}{b \times c}$$

3. Therefore, the calculation is done by placing the numbers in the 4 x 4 table in step 1 and using the formula in step 2 to calculate the numbers
4. For example, if the data in a cross-sectional study show that of 100 smokers 20 had cancer and of 100 non-smokers 10 had cancer then the 4 x 4 would be:

	Smoker	Non-Smoker	Total
Cancer	20	10	30
Healthy	80	90	170
Total	100	100	100

And the OR would be calculated as follows:

$$\text{OR} = \frac{a \times d}{b \times c} = \frac{20 \times 90}{80 \times 10} = \frac{1800}{800} = 2.25$$

5. Alternatively, in a case control study were the data indicate that of 30 cancer participants, 20 were smokers and of 170 non-cancer (healthy) participants, 80 were smokers then the 4 x 4 would be populated by entering a and c and the totals and then calculating b (b=30-20=10) and d (d=170-80=90), therefore the OR would be the same.

	Smoker	Non-Smoker	Total
Cancer	20	b	30
Healthy	80	d	170
Total	100	b+d	100

Appendix J: MeSH terms used for consanguinity search

Search was conducted on 21.04.2015

Number of records retrieved for each term in parenthesis

- 1 Consanguinity (10217)
- 2 CSG marriage (9110)
- 3 Cousin marriage (8906)
- 4 Cousin adj3 marriage).mp. (114)
- 5 1 or 2 or 3 or 4 (10479)
- 6 Female Fertility (84496)
- 7 Female Infertility (24491)
- 8 Fertility (75633)
- 9 Infertility (68168)
- 10 6 or 7 or 8 or 9 (128384)
- 11 5 AND 10 (452)
- 12 Remove duplicates from 11 (439)

Appendix K: MeSH terms used for FGM/C search

Search was conducted on 21.04.2015

Number of records retrieved for each term in parenthesis

- 1 Female genital mutilation (1825)
- 2 FGC (600)
- 4 Female circumcision or Circumcision, Female/ (2562)
- 5 Female genital cutting (359)
- 6 Circumcision, Female/ or FGM (2145)
- 7 1 or 2 or 3 or 4 or 5 or 6 (4035)
- 8 Female Fertility (10705)
- 9 Female Infertility (52391)
- 10 Fertility (185000)
- 11 Infertility (171253)
- 12 8 or 9 or 10 or 11 (317804)
- 13 7 AND 12 (187)
- 14 Remove duplicates from 13 (164)

Appendix L: MeSH terms used for HIV search

Search was conducted on 22.11.2015

Number of records retrieved for each term in parenthesis

- 1 Infertility (200945)
- 2 Female infertility (65863)
- 3 Fertility (191806)
- 4 Female fertility (10938)
- 5 1 or 2 or 3 or 4 (348959)
- 6 Human immunodeficiency virus (243280)
- 7 Acquired immune deficiency syndrome [Complication, Diagnosis, Disease Management, Drug Resistance, Drug Therapy, Epidemiology, Etiology, Radiotherapy, Rehabilitation, Side Effect] (49677)
- 8 6 or 7 (282734)
- 9 5 AND 8 (922)
- 10 NOT Neoplasm (805)
- 11 NOT Practice guideline (777)
- 12 NOT medical ethics or ethics (726)
- 13 NOT intrauterine contraceptive device (701)
- 14 NOT Tuberculosis/ or urogenital tuberculosis (685)
- 15 NOT Monitoring (671)
- 16 NOT Embryo transfer/ or fertilization in vitro/ or intracytoplasmic sperm injection (564)
- 17 Remove duplicates from 16 (514)

Appendix M: MeSH terms used for genital tuberculosis (GTB) search

Search was conducted from on 19.01.2016

Number of records retrieved for each term in parenthesis

- 1 Infertility (172200)
- 2 Female Infertility (28296)
- 3 Fertility (184811)
- 4 Female Fertility (10773)
- 5 1 or 2 or 3 or 4 (318509)
- 6 Genital TB (490)
- 7 Genital tuberculosis (2757)
- 8 6 or 7 (3093)
- 9 5 AND 8 (546)
- 10 remove duplicates from 9 (378)

Appendix N: MeSH terms used for bacterial vaginosis (BV) search

Search was conducted on 27.08.2016

Number of records retrieved for each term in parenthesis

- 1 Infertility (166798)
- 2 Fertility (104796)
- 3 Female infertility (66936)
- 4 Female fertility (8766)
- 5 1 or 2 or 3 or 4 (255953)
- 6 bacterial vaginosis (7148)
- 7 5 AND 6 (167)
- 8 remove duplicates from 7 (129)

Appendix O: MeSH terms used for Dilatation and Curettage search

Search was conducted on 05.02.2016

Number of records retrieved for each term in parenthesis

- 1 Infertility (161414)
- 2 Infertility, Female (65023)
- 3 Fertility (101253)
- 4 Fertility/ or female fertility.mp. (102707)
- 5 1 or 2 or 3 or 4 (248762)
- 6 Dilatation and curettage (4904)
- 7 limit 6 to humans (4420)
- 8 5 AND 7 (237)
- 9 remove duplicates from 8 (210)

Appendix P: Patient Interview Materials

A. Procedure

Step 1: Briefing and consent form

Step 2: Background information

- Administer the 16-item Background Information Form

Step 3: FertiQoL (not reported in this thesis)

Step 4: Questions regarding fertility awareness

- Assess whether the participant knows about the following:
 - Signs, symptoms of fertility problems
 - Preventable causes of fertility problems
 - When to seek help if they have trouble becoming pregnant

Step 5: Desire to know about fertility

- Ask if the participant would value knowing more about these aspects of fertility?

Step 6: Administration of FertiSTAT

- Administer the adapted FertiSTAT checklist (Arabic version)

Step 7: Questions about FertiSTAT

- Ask open ended questions to assess the following:
 - How they talk about fertility health to others and what is their preferred language of communication for sensitive topics
 - Potential format of administration (e.g., specific format, setting, source and time required for administration)
 - Would they have wanted to know this information in the past?
 - How useful would it have been to have this information and when?

Step 8: Debrief

B. Consent Form for FertiQoL and FertiSTAT Interviews

Consent form (to be read or read out)

I understand that my participation in this project will involve a ‘think-aloud’ task during which I will provide my thoughts and feelings about the FertiSTAT and FertiQoL while completing the tools. I will then be asked to complete a short interview and a questionnaire about my demographics (e.g., age, education). The whole study should take around 60 to 90 minutes to complete.

I understand that participation in this study is entirely voluntary and that I can withdraw from the study at any time without giving a reason.

I understand that I am free to ask any questions at any time. I am free to withdraw or discuss my concerns with the researcher Rasha Bayoumi (bayoumir@cardiff.ac.uk).

I understand that the think-aloud task and interview will be audio-recorded so that the topics raised can be transcribed and synthesised. The information provided by me will be stored on a password-protected computer that belongs to the researcher Rasha Bayoumi and Prof Jacky Boivin and will be held anonymously, so that it is impossible to trace this information back to me individually. Once the recording of the session has been transcribed the recording will be deleted and the transcribed data and questionnaire responses will be retained indefinitely.

I also understand that at the end of the study I will be provided with additional information and feedback about the purpose of the study.

I, _____(NAME) consent to participate in the study conducted by Rasha Bayoumi, School of Psychology, Cardiff University with the supervision of Professor Jacky Boivin.

Signed:

Date:

Arabic Consent form

استمارة الموافقة (أن تقرأ أو تقرأ)

أنا أفهم أن مشاركتي في هذا المشروع تتضمن مهمة تقديم أفكار ومشاغري حول FertiSTAT وFertiQoL أثناء الأداة. سيتم بعد ذلك إكمال مقابلة قصيرة واستبيان عن معلوماتي الديموغرافية (على سبيل المثال، العمر، والتعليم). سوف تأخذ الدراسة بأكملها حوالي 60 إلى 90 دقيقة للإكمال. وأنا أفهم أن مشاركتي في هذه الدراسة طوعية تماما وأستطيع الانسحاب من الدراسة في أي وقت دون إبداء أسباب وأنا حر أن أسأل أي سؤال في أي وقت. أنا حر في الانسحاب أو مناقشة مخوفي مع الباحثة رشا بيومي (bayoumir@cardiff.ac.uk).

أنا أفهم أن المقابلة ستكون مسجلة حتى يمكن نسخها وتوليها. سيتم تخزين المعلومات التي قدمتها على جهاز كمبيوتر (محمي بكلمة مرور) المملوك لدى الباحثة رشا بيومي والأستاذ جاكى بوافين وسيعقد مجهول، بحيث أنه من المستحيل أن تتبع هذه المعلومات لي على حدة. وبمجرد أن يتم نسخ تسجيل المقابلة سيتم حذف التسجيل وسيتم الاحتفاظ بالبيانات والردود على الاستبيان إلى أجل غير مسمى.

أفهم أيضا أنه في نهاية الدراسة ستقدم لي معلومات حول الغرض من الدراسة.

أنا، _____ (الاسم) موافق على المشاركة في الدراسة التي أجرتها رشا بيومي (كلية علم النفس، جامعة كارديف مع إشراف البروفيسور جاكى بوافين).

التوقيع:

التاريخ:

C. Background Information Form for Interviews

1. Patient number _____
2. Age _____
3. Sex _____
4. Address _____
5. Occupation _____
6. Education:
 - Illiterate:
 - Primary level:
 - Secondary level:
 - More than secondary level:
7. Duration of marriage _____
8. Duration of couple living together _____
9. Menstruation:
 - Normal
 - Not normal
10. If menstruation is not normal:
 - No period > 6 months
 - No period < 6 months
 - Increase in the amount of menstruation
 - Decrease in the amount of menstruation
11. Painful intercourse
 - YES
 - NO
12. Medical and surgical history:
 - Blood pressure (hypertension)
 - Thyroid disease
13. Have you been pregnant before:
 - YES
 - NO
14. Number of previous pregnancies _____
 - Without treatment _____
 - With ovarian stimulation only _____
 - With ART _____
15. Duration of delay in pregnancy _____
16. Reasons for delay in pregnancy:
 - Husband
 - Wife
 - Both
 - Unknown

D. FertiSTAT Checklist for signs, symptoms and risk factors for fertility problems (tentative English version)

Woman

How old are you? _____ years

How long have you been trying to become pregnant? _____ years: months

Please indicate if any of the following reproductive health issues relate to your situation: (tick all that apply)

- Severe period pains
- My period is unpredictable (can be more than 5 days early or late)
- My period lasts less than 21 days (no contraception)
- My period lasts more than 35 days (no contraception)
- I do not have a period
- I have had surgery in my abdominal region
- I suffer from endometriosis
- I have had pelvic inflammatory disease (PID) (a serious infection in my uterus that required more than just one prescription of antibiotics)

Please indicate if you have been diagnosed with any of the following medical conditions, infections or diseases: (tick all that apply)

- Diabetes
- Cancer
- Kidney disease
- Sickle cell anaemia
- Thyroid disease
- Lupus
- Tuberculosis
- Genital tuberculosis
- HIV or HIV/AIDS
- Bacterial vaginosis

Please indicate if these conditions define your situation: (tick all that apply)

- I have been cut (Female genital cutting)
- I am married to a blood relative

Please indicate if your lifestyle includes any of the following situations: (tick all that apply)

- I smoke frequently (>10 cigarettes per day) (water-pipe, chewing tobacco)
- I can't cope with stress I'm currently experiencing
- I drink >14 units alcohol per week (14 glasses of wine, 28 beers (1/2 pint) or 14 shots of spirit)
- I drink >7 units caffeine per day (7 cups of coffee or 14 cups of tea or 14 sodas)
- I smoke marijuana frequently (>4 time per week)
- I have had an STI
- I'm more than 13kg (28 lb) overweight
- I have unprotected sex with multiple partners
- I have used a class A drugs in the past (heroin, cocaine, ecstasy)
- I'm currently taking anabolic steroids (for non-medical uses)

Man

How old are you? _____ years

How long have you been trying with your partner to become pregnant? _____ years: months

Please indicate if any of the following issues relate to your situation: (tick all that apply)

- I had the “mumps” as a child (before puberty)
- I have an undescended testicle
- I am married to a blood relative
- I have or had been diagnosed with tuberculosis
- I have or had been diagnosed with genital tuberculosis
- I have been diagnosed with HIV or HIV/AIDS
- I have or had been diagnosed with cancer

Please indicate if your lifestyle includes any of the following situations: (tick all that apply)

- I smoke frequently (>10 cigarettes per day) (water-pipe, chewing tobacco)
- I can't cope with stress I'm currently experiencing
- I drink >14 units alcohol per week (14 glasses of wine, 28 beers (1/2 pint) or 14 shots of spirit)
- I drink >7 units caffeine per day (7 cups of coffee or 14 cups of tea or 14 sodas)
- I smoke marijuana frequently (>4 time per week)
- I have had an STI
- I have unprotected sex with multiple partners
- I have used a class A drugs in the past (heroin, cocaine, ecstasy)
- I'm currently taking anabolic steroids (for non-medical uses)

FertiSTAT (tentative English version)**FertiSTAT أداة فحص للعلامات والأعراض وعوامل الخطر لمشكلات الخصوبة****للنساء**

كم عمرك؟ _____ سنوات
منذ متى وأنت تحاولين أن تصبح حاملاً؟ _____ سنوات : أشهر

يرجى بيان ما إذا كان أي من مشكلات الصحة الإنجابية التالية تتعلق بوضعك: (ضعي علامة على كل ما ينطبق)

- آلام الدورة الشهرية الشديدة
- فترة الدورة الشهرية لا يمكن التنبؤ بها (يمكن أن تأتي قبل موعدها أو تتأخر عن موعدها بأكثر من 5 أيام)
- الدورة الشهرية تستمر لأقل من 21 يوماً (بدون وسائل منع الحمل)
- الدورة الشهرية تستمر أكثر من 35 يوماً (بدون وسائل منع الحمل)
- ليس لدي دورة شهرية
- أنا خضعت لعملية جراحية في منطقة البطن
- أعاني من الانتباز البطاني الرحمي (البطانة المهاجرة)
- لقد عانيت من مرض التهاب الحوض (عدوى خطيرة في الرحم تطلبت أكثر من وصفة طبية واحدة من المضادات الحيوية)

يرجى بيان ما إذا كنت قد تم تشخيصك بأي من الحالات الطبية، والتهابات أو الأمراض التالية : (ضعي علامة على كل ما ينطبق)

- داء السكري
- سرطان
- مرض الكلى
- فقر الدم المنجلي
- مرض الغدة الدرقية
- الذئبة
- مرض السل
- السل التناسلي
- فيروس نقص المناعة البشرية أو الإيدز.
- التهاب المهبل البكتيري

يرجى بيان ما إذا كانت هذه الشروط تنطبق على وضعك الخاص: (ضعي علامة على كل ما ينطبق)

- لقد خضعت لختان الإناث
- أنا متزوجة من أحد أقاربي

يرجى بيان ما إذا كان نمط حياتك يشمل أيًا من الحالات التالية: (ضعي علامة على كل ما ينطبق)

- أَدخِن كثيرًا (>10 سجائر يوميًا) (المرجيلة، ومضغ التبغ)
- لا أستطيع التعامل مع الضغط النفسي الذي أعاني منه في الوقت الحالي
- أشرب <14 وحدة الكحول في الأسبوع (14 كأسًا من النبيذ، 28 وحدة بيرة (نصف بينت (236 مللي لتر)) أو 14 كأسًا صغيرًا من المشروبات الروحية)

- أشرب <7 وحدات الكافيين يوميا (7 أكواب من القهوة أو 14 أكواب من الشاي أو 14 مشروبات غازية)
- أذخن الماريجوانا في كثير من الأحيان (<4 مرات في الأسبوع)
- سبقت لي الإصابة بأحد الأمراض المنقولة جنسيا.
- عندي زيادة في الوزن بأكثر من 13 كيلو غراما (28 رطلاً)
- مارست الجنس دون وقاية مع عدة أشخاص
- لقد استخدمت/تعاطيت المخدرات (العقاقير من فئة A) في الماضي (الهيروين والكوكايين وحبوب الهلوسة)
- أنا حالياً أتعاطي المنشطات (للاستخدامات غير الطبية)

للرجال

كم عمرك؟ _____ سنوات
منذ متى وأنت تحاول مع شريكة حياتك لتصبح حاملاً؟ _____ سنوات: أشهر

يرجى بيان ما إذا كانت أي من المشكلات التالية تنطبق على وضعك الخاص: (ضع علامة على كل ما ينطبق)

- عانيت من "النكاف" (ابو عديلات) عندما كنت طفلاً (قبل البلوغ)
- لدي خصية معلقة (غير نازلة)
- أنا متزوج من أحدي قريباتي
- تم تشخيصي حالياً أو في الماضي بمرض السل
- تم تشخيصي حالياً أو في الماضي بمرض السل التناسلي
- تم تشخيصي حالياً أو في الماضي بمرض بفيروس نقص المناعة البشرية أو الإيدز
- تم تشخيصي حالياً أو في الماضي بمرض بالسرطان

يرجى بيان ما إذا كان نمط حياتك يشمل أيًا من الحالات التالية: (ضع علامة على كل ما ينطبق)

- أذخن كثيراً (<10 سجائر يوميا) (الرجلية، ومضغ التبغ)
- لا أستطيع التعامل مع الضغط النفسي الذي أعاني منه في الوقت الحالي
- أشرب <14 وحدة الكحول في الأسبوع (14 كأساً من النبيذ، 28 وحدة بيرة (نصف بينت (236 مللي لتر)) أو 14 كأساً صغيراً من المشروبات الروحية)
- أشرب <7 وحدات الكافيين يوميا (7 أكواب من القهوة أو 14 أكواب من الشاي أو 14 مشروبات غازية)
- أذخن الماريجوانا في كثير من الأحيان (<4 مرات في الأسبوع)
- سبقت لي الإصابة بأحد الأمراض المنقولة جنسيا
- مارست الجنس دون وقاية مع عدة أشخاص
- لقد استخدمت/تعاطيت المخدرات (العقاقير من فئة A) في الماضي (الهيروين والكوكايين وحبوب الهلوسة)
- أنا حالياً أتعاطي المنشطات (للاستخدامات غير الطبية)

E. Semi-Structured Interview Topic guide

(Only questions pertaining to FertiSTAT included)

Question	Section
	Section 1: Fertility Knowledge (before administering the FertiSTAT)
1	Do you know about the signs and symptoms of infertility?
2	What are some signs and symptoms that you know? (if not understood, explain)
3	Do you have info about the risk factors that people can avoid? (if not understood, explain)
4	What are some risk factors that you know?
5	Do you know when a person should consult a doctor for delayed pregnancy?
6	Would you like to know more about the signs, symptoms, preventable risk factors and when to seek help?
	Section 2: Questions about FertiSTAT (after administering the FertiSTAT)
	A. Benefit of FertiSTAT
7	Where you aware of this information before?
8	What information is new to you?
9	Would you have wanted to know this information in the past?
10	Do you think this information is important for people to know, here in Sudan, or is it unrelated to our society?
11	How useful would it have been to have this information and when?
12	Is this information beneficial?
13	In what way is this information beneficial?
	B. Format, setting, source and target population (if unable to generate spontaneously, give examples)
14	Where can people get this information from? What is the best setting?
15	Who is the best person to convey this type of information?
16	How can this information be conveyed?
17	What if you find it in a magazine or a newspaper, would that be acceptable?
18	When is the best timing to present this information?
19	What age is this information most appropriate for?
20	Should the information be given before or after marriage?
	C. Sensitive topics in FertiSTAT
21	We have been told that some of the topics in the FertiSTAT may not be acceptable in our society, that there are things we shouldn't say, what do you think?
22	What about information about things like drugs, alcohol and sex, how acceptable would it be to talk about them in our society?
23	Is it better to talk about these sensitive topics or to avoid them?
24	What would be the best way to talk about these topics?

F. Debrief for FertiQoL and FertiSTAT Interviews

One of the most important issues in determining health is how we perceive our own health and illness. Successful public health campaigns have used a strategy of increasing public awareness of certain illnesses by researching the relevant health indicators for each illness, ensuring most people are aware of the signs and symptoms of the diseases (e.g., cancer, heart disease). Such research has highlighted that this can be used to monitor needs for health care, and evaluate the effectiveness and impact of health care programs.

The majority of couples will get pregnant after trying for 12 months. However, for a small number of couples it may take longer. There has been little research highlighting the main indicators for those that might take longer to get pregnant. In addition few people know the signs of reproductive disease or the risk factors for fertility difficulties. A tool was developed to raise awareness about risk factors for fertility problems and provide women with information on what to do when they have any risks. We also developed a quality of life tool called the FertiQoL. However, we do not know whether these tools can be used in countries other than the one where it was developed. We asked you to give us your thoughts and feelings about the FertiSTAT and answer questions in an interview and questionnaire to enable us to evaluate whether these could be used at this and other clinics in Sudan.

It was important to ask a range of personal questions about your lifestyle and reproductive history and we would like to assure you that all the data you provided will be held anonymously and it will not be possible to trace the information back to you. Data will be stored on a computer that is password-protected and belongs to Rasha Bayoumi and Prof Jacky Boivin.

If participation in the study has caused concern about your health then please contact your doctor in the usual way or this Facebook page – OBGYN consultations, that provides support to women with fertility problems.

If you have any further questions about this research then please let Rasha Bayoumi or your doctor know of these concerns and they will inform Prof Jacky Boivin.

School of Psychology
Cardiff University
Tower Building, Park Place
Cardiff, Wales
CF10 3AT
boivin@cardiff.ac.uk

Professor Jacky Boivin is interested in the psychosocial aspects of reproductive health. She has conducted many studies in this area on issues such as the link between stress and fertility, differences between men and women in emotional reactions to fertility issues, whether counselling helps people cope with fertility problems, how children conceived with fertility treatment develop, and much more.

This research has been carried out with the help of women from many countries worldwide. You can see some of the published reports of this work on www.cardiffertilitystudies.com.

Psychology Ethics committee details:

Email: psychethics@cf.ac.uk

Phone: +44 (0)29 208 74007, Fax: +44 (0)29 2087 4858. Address: Psychology Ethics Committee Secretary.

Arabic Debrief

استجوب (شرح الغرض من المقابلة والاستبيانات)

واحدة من أهم القضايا في تحديد الصحة هي الطريقة التي ننظر بها لصحتنا و الأمراض. وقد استخدمت حملات الصحة العامة الناجحة استراتيجية لزيادة الوعي عن بعض الأمراض عن طريق البحث في المؤشرات الصحية المناسبة لكل مرض، وضمان أن معظم الناس يدركون علامات وأعراض الأمراض (مثل السرطان وأمراض القلب). وقد أبرزت هذه البحوث أن هذا النهج يمكن استخدامه لرصد احتياجات الرعاية الصحية، وتقييم مدى فعالية وتأثير برامج الرعاية الصحية. بالنسبة لغالبية الأزواج يحدث الحمل بعد المحاولة لمدة اثني عشر شهرا. ومع ذلك، لعدد من الأزواج قد يستغرق وقتا أطول. هناك القليل من الأبحاث عن المؤشرات الرئيسية لتأخر الحمل. وبالإضافة إلى ذلك قلة من الناس تعرف علامات المرض التناسلي أو عوامل صعوبات الخصوبة. وقد تم تطوير أداة لرفع مستوى الوعي حول عوامل الخطر لمشاكل الخصوبة وتزويد النساء بالمعلومات حول ما يجب القيام به عندما يكون لديهم أي مخاطر. نحن أيضا قمنا بتطوير أداة/استبيان حول نوعية الحياة يسمى FertiQoL. ومع ذلك، فإننا لا نعرف ما إذا كانت هذه الأدوات يمكن أن تستخدم في بلدان غير حيث تم وضعها.

طلبنا منك أن تعطينا أفكارك ومشاعرك حول FertiSTAT والإجابة على الأسئلة في المقابلة والاستبيان لنتمكن من تقييم ما إذا كانت هذه الاستبيانات يمكن استخدامها في هذه العيادة وغيرها من العيادات في السودان.

كان من المهم طرح مجموعة من الأسئلة الشخصية حول نمط حياتك وتاريخ الإنجاب، ونود أن نؤكد لكم أن جميع البيانات التي قدمتها ستعقد مجهول، وأنه لن يكون من الممكن تتبع المعلومات مرة أخرى لك. سيتم تخزين البيانات على جهاز كمبيوتر (محمي بكلمة مرور) وينتمي إلى/المملوك لدى رشا بيومي والأستاذ جاكى بوافين.

إذا كان الاشتراك في هذه الدراسة قد تسبب في القلق بشأن صحتك الرجاء الاتصال بالطبيب بالطريقة المعتادة أو عن طريق صفحة الفيسبوك – استشارات أمراض النساء والتوليد و الخصوبة، التي توفر الدعم للنساء الذين يعانون من مشاكل الخصوبة.

إذا كان لديك أي أسئلة أخرى حول هذا البحث اسأل رشا بيومي أو طبيبك عن هذه المخاوف، وأنهم سوف إبلاغ الأستاذ جاكى بوافين.

كلية علم النفس

جامعة كارديف

برج البناء، بارك بليس

كارديف، ويلز

CF10 3AT

boivin@cardiff.ac.uk

أستاذة جاكى بوافين تهتم بالجوانب النفسية والاجتماعية للصحة الإنجابية. وقالت إنها أجرت العديد من الدراسات في هذا المجال على قضايا مثل العلاقة بين التوتر والخصوبة، والاختلافات بين الرجال

والنساء في ردود الفعل العاطفية لقضايا الخصوبة، إذا الإرشاد يساعد الناس على التكيف مع مشاكل الخصوبة، نمواً أطفال الانابيب، والكثير.

وقد تم تنفيذ هذا البحث مع مساعدة نساء من العديد من البلدان في جميع أنحاء العالم. يمكنك ان ترى بعض التقارير التي نشرت على www.cardiffertilitystudies.com.

تفاصيل لجنة الأخلاق بكلية علم النفس:

البريد الإلكتروني: psychethics@cf.ac.uk

الهاتف: +44 (0) 29 208 74007 فاكس: +44 (0) 29 2087 29 4858. العنوان: أمين سر لجنة الأخلاق بكلية علم النفس.

Appendix Q: Ethics Approval for Patient Interviews in a Sample of Sudanese Couples Attending at an Infertility Clinic

The Ethics Committee has considered the amendment to your Generic Staff project proposal: Fertility Health Issues (EC.07.05.01.1284GR3A7).

The amendment has been approved.

Please note that if any changes are made to the above project then you must notify the Ethics Committee.

Best wishes,
Mark Jones

School of Psychology Research Ethics Committee
Cardiff University
Tower Building
70 Park Place
Cardiff
CF10 3AT

Appendix R: Themes, sub-themes and illustrative quotes from the interviews with fertility patients in Sudan

Themes	Sub-themes	Illustrative quotes
Desire for fertility info		<p>RB: OK, do you feel you want to know more info about this topic?</p> <p>13: I feel like I know about it, but when I get a desire to know more.</p> <p>RB: Ok, do you feel you want to know more about these things?</p> <p>5: yes, I'm currently searching (for info).</p>
State of fertility knowledge in this sample	What is known	<p>13: Walahi, since we have been alive we know of cutting that there is the Sunna one and the pharaonic one. And we are all cut Sunna, something very minimal, something that wouldn't have an impact in the future. But in general I have seen people who are cut pharaonic that really face problems.</p> <p>14: that's why they can have problems unrelated to age, young women can have problems too.</p> <p>RB: explained age and time trying</p> <p>20: yes after 35 the chance is weak, very weak (slim)</p> <p>12: there are medical conditions that prevent pregnancy.</p> <p>13: (...) Infections, for example if you get infections and you are unaware of it</p> <p>RB: were you aware of this info in the past?</p> <p>1: yes, especially drugs, coffee, fizzy drinks (caffeinated beverages), I know that, I have even reduced it (her consumption).</p> <p>RB: what about when to go to the doctor, when you have a fertility problem?</p> <p>1: when you are married more than 2 years, and you're completely settled (residing together). When he's in a country and you another country, when there has been a previous pregnancy and miscarriage.</p> <p>16: I think if residing together then after 1 year should go to the doctor, so that they (doctors) can give stimulants (ovulatory) or if there is infection they can get treated</p> <p>RB: what about when to go to the doctor?</p> <p>5: after one year of marriage and no pregnancy, if the age is more than 34 years</p> <p>RB: Exactly, so do you know when a girl should visit the doctor?</p> <p>13: I would say a year is good, because of life circumstances and difficulties, you find that your husband is settled with you (spending enough time together to allow for having sex regularly) during your honeymoon and then every day after that there are errands and stuff, you know life is really difficult. So up to a year they can be waiting for the natural (conception). After that they have to find out what's the problem.</p>
	What is not known	<p>RB: how much do you feel you know about fertility generally and your case (particularly)?</p> <p>1: I feel I have little info.</p> <p>RB: do you have any info about the risk factors, the things that can cause fertility problems?</p> <p>2: No, I don't know.</p> <p>RB : when to seek help is related to age, so if a women is less than 34 years she should go after 1 yr but if she is older than 34 she should only wait 6 months, because fertility declines after 34, were you aware of the impact of age?</p> <p>17: no I didn't know, especially the specific age I didn't know that.</p>
	Misconception s/myths	<p>RB: Ok, do you know about the risk factors one can avoid so as not to get fertility problems?</p> <p>13: this thing, you mean before marriage? The most important thing, for example, taking care of the health of your reproductive system, cleanliness and things like that.</p> <p>13: or your hygiene is not good, this is something that in the end can lead to for example other things, like in the uterus, in the ovaries in the pelvis, and in this way, you will have problems.</p> <p>14: [I don't know, I got married at 32 and I came back from my honeymoon I was pregnant.]</p> <p>14: And sometimes it's the other way around, people get married much older and mashallah they have 2 or 3 kids. So, there is a chance.</p> <p>14: For me, I mean honestly, when I went for my laparoscopy, when I came to the clinic here, I know the problem they tell you about aging, getting older, delayed marriage, but I find girls in their 20s (in the clinic).</p> <p>16: do you mean what causes not having kids or what? For a woman?</p> <p>RB: yes.</p> <p>16: walahi cysts (ovarian) always.</p> <p>12: walahi, emotional pressure (stress) may affect a women or a man. Emotional pressure is one of them (risk factors).</p>
Benefits of fertility education	Perceived personal	<p>4: yes, I didn't know this information.</p>

Themes	Sub-themes	Illustrative quotes
	benefit (to self)	5: very much, it's the first time I know that it (FS items) can have an impact on fertility.
	Perceived general benefit (to others)	11: of course, it's important that they know.
	Utility of the tool: addresses knowledge gap and encourage behaviour change	13: very beneficial, they have to, they have to know it. 17: (...) Our society is in need of lots of raised awareness A LOT!! RB: meaning, when would this info have been useful to you? 16: walahi from early on is better so I can avoid things like drinking too much coffee and tea and things like that.
		13: To see where there are gaps and to fill them. 5: yes they should know, because there are people who drink lots of coffee and such. 14: Or a woman at home if she feels her son wants to use chewing tobacco, she can do a bit of control, to show him this thing what it does later (the effect of tobacco in the long run).
Specific suggestions for the tool	Content: taboo topics	RB: what about the sensitive topics, what's the best way for people to talk about it? 2: sex, drinking (alcohol)? Ask aadee (normally, casually). 1: depends on the people, some people consider these issues 3aib (culturally unacceptable), and other people see there is no gilat adab (disrespectful, rude) or that this person is wakiha (impolite, has no shame). 7: people should talk about it aadee (normally), because it's for their benefit. 3: a person should explain aadee (normally) no problem. 17: they prefer if it's a woman, not sure why, but when it's a woman they feel relaxed and can understand. 4: people may not accept these subjects, and I won't be able to face them regarding certain issues. 4: not all of them, some people don't like to talk, to tell you their life story, not even in here, gesturing to indicate the clinic, about why or what's happening to them, not all people. 19: walahi, if you introduce yourself properly in the beginning and they see you are a doctor, a professional, a person would have their presences (the word she used 'haibtoo' suggests a dominant presence). 19: well with the rule of customs (the rules dictated by culture) ... (looks like she is thinking), but I don't think so, maybe in the olden days maybe, but now its aadee (normal, acceptable). RB: well, we have been told that there are people in our society that will not accept this, that there are things we shouldn't say because they are unacceptable in our society. So, is it better to say or not to say? 14: walahi, you should say it because someone will accept it and benefit.
	Format	RB: what if you find it in a magazine or a newspaper. 13: yes, for example, yes I can do it. No, no aadee (normal and acceptable), especially if it is anonymous. 14: walahi, this newspaper, I see, I think people here get the news from the internet, the newspaper, just the old people, because they are used to this 'cross your legs and put on your glasses'. But in general, for people, the news info comes to them, newspapers, are not that much. RB: but people would accept to talk about FGM and sex, this won't be difficult? 12: no it's not difficult, it could be specifically for women, a seminar just for women so they can ask. 19: walahi something printed the boys will not read it, I'm talking about my brothers at home, from my experience, but if its lectures or seminars, or they went to the schools and universities, this way they will accept it, this way they will listen, because a boy by nature wants to hear not to read. 1: clear and direct questions so that the answer is clear and direct. 18: but there is something! This WhatsApp (a social media app that is very popular in Sudan and the Middle East), lately, people have really been concentrating on it, that is, if this info was on WhatsApp and Facebook they will read it but not a hardcopy. RB: so what is the best way for us to get them to answer and give us this info in a suitable way, how?

Themes	Sub-themes	Illustrative quotes
		<p>1: via questions, from the beginning you will get a sense of whether this person is willing to accept things, or not accept. For example, this sex question, most people will say 'enough I don't want to (continue)'. 12: it could be specifically for women, a seminar just for women so they can ask RB: so they can ask questions. 12: yes, a specific place where they can ask, women's questions, what's happening to you.</p>
	Setting	<p>13: I imagine the home to be the best context, I mean the most important role, one sees their father and their mother and how they are, it's better that they show them. 12: yes, it would work in schools. RB: but it wouldn't work if a doctor (feminine) came to places in the villages, one (feminine) comes and tells the people or something? 12: yes, it's possible, it's possible yes. 17: training course within schools and universities. 14: walahi, I imagine raising awareness can be in schools, if they put it as leaflets/handouts that would be useful. 14: It can be put out in clinics, so when you're, when you're done you can take it with you. It can be left at the mosque. RB: Ok so they won't accept it, so what do you think is the best way, I mean if they are not going to accept this, how do we deliver this info? 20: for girls I think they should know this info from school.</p>
	Source	<p>11: the best time is from the treating physician to the patient and the co-patient. When he is delivering (the info), they are there, he can deliver this info to them, he is the most trusted person. 1: Talk in the way that makes you feel comfortable with people, the person you feel comfortable with and understands you, a person who understands the issue. 19: yes it makes no difference because in the end she has the info. The real difference lies in whether the info is given by a specialist, not man or woman, for me personally makes no difference. 13: it seems that it's always the case that if you trust the source (person) that the info is coming from them, that's better. But if it comes from someone I don't trust, I will just leave him and go. RB: so it's better if a woman comes and talks to the girls and she can tell them and show them? 10: why not... a man, for example, I can't ask him questions, but you are a woman like me so I can ask you questions. RB: OK, is it better for this info to come from a doctor or students like us for example, from a woman or a man? Who is the most suitable person to provide this info? 10: from a doctor or a student like you, they teach it to you so you can show it to people. RB: OK, what if the father and the mother don't have the info, where do they get this info? 13: it's better if the school, the teachers. 12: the responsible 'al gehat' [entities], the mother. 12: the educated sisters, relatives (feminine) for example, some of them are educated. 10: your mother, older sister at home. 10: from a doctor or a student like you, they teach it to you so you can show it to people. 11: the best time is from the treating physician to the patient and the co-patient. When he is delivering (the info), they are there, he can deliver this info to them, he is the most trusted person. So when you bring this questionnaire a lot of people will give you false info, but they trust the doctor, they will not lie to him at all, they will understand what he's saying.</p>
	Timing	<p>RB: when should they give her info like this? 10: leave her till she grows up. RB: not necessarily after marriage? 12: no, not necessarily after marriage, she can know this from when she is a teenager. RB: when should they be given this info? 17: it should be given to youngsters, before they get married. RB: meaning, when would this info have been useful to you? 16: walahi from early on is better so I can avoid things like drinking too much coffee and tea and things like that. 5: the first stage of high school, 17 or 20 years. 19: when they are in the engagement period, approaching marriage, they should be given this info. 18: I think at puberty they should be made aware of these things.</p>

Themes	Sub-themes	Illustrative quotes
		<p>13: it's better if the school, the teachers, there should be something like this, this type of raising awareness, infectious diseases (STIs). When one reaches this stage, there is no more embarrassment, he should hear this thing before he falls into it (the behaviour).</p> <p>RB: ok so can you help us here, what is the best time and way?</p> <p>11: the best time is from the treating physician to the patient and the co-patient. When he is delivering (the info), they are there, he can deliver this info to them</p>
Factors influencing implementation	Personal preferences (endorsed)	<p>1: depends on the people, some people consider these issues 3aib (culturally unacceptable), and other people see there is no gilat adab (disrespectful, rude) or that this person is wakiha (impolite, has no shame).</p> <p>6: walahi, it depends, people are different, some people aadee (with ease) will accept it, no problem.</p> <p>1: from the beginning you will get a sense of whether this person is willing to accept things, or not accept. For example, this sex question, most people will say 'enough I don't want to (continue)'.</p> <p>1: yes they will benefit, it's choices, you don't like the page, you turn it and continue the rest.</p>
	Perceived benefit (endorsed)	<p>14: walahi, you should say it because someone will accept it and benefit.</p> <p>4: no it's not difficult, if people accept it (are willing to accept it), the topic is not that difficult, it's just info that one can benefit from.</p> <p>1: cons, there are no cons for me, the topic is normal, the pros is that it increases education (not scholastic in nature).</p> <p>2: yes I would look at it, I would find it beneficial.</p> <p>7: yes, I would complete it, because this is a useful thing for people, one would do it.</p> <p>14: thank you so much, this has been so helpful.</p>
	Acknowledging the benefit of education/info (participant generated)	<p>13: questionnaires in general are beneficial because the person is studying this thing and wants to help us benefit from it. To see where there are gaps and to fill them. So no problem.</p> <p>1: clear and direct questions so that the answer is clear and direct, you benefit and I benefit.</p> <p>17: yes, they can benefit, if you know you will benefit, like training course, where I work we do education and training course and people have learned a lot understood a lot.</p>
	The appropriate method of distribution (participant generated)	<p>17: lectures given by doctors, health visitors, or even lectures through ministries e.g. ministry of agriculture has meetings, they visit places and have workshops to raise awareness of citizens.</p> <p>14: Or if everyone who comes to the clinic takes one, everyone who goes to the mosque takes one, the info will be delivered.</p> <p>14: walahi if it (FertiSTAT) is distributed right.</p>
	Persistence (participant generated)	<p>RB: so, you're saying even if they say they don't accept it we should give it anyway?</p> <p>14: I told you, he will calculate it (risk level) in his head. He might think maybe this is right, he will do it himself (fill out the FS).</p>
Challenges and barriers to implementation	'Others' will not accept taboo topics	<p>1: cons, there are no cons for me, the topic is normal</p> <p>RB: do you think people will respond authentically?</p> <p>1: no (...) from the beginning you will get a sense of whether this person is willing to accept things, or not accept. For example, this sex question, most people will say 'enough I don't want to (continue)'</p> <p>4: people may not accept these subjects, and I won't be able to face them regarding certain issues.</p> <p>RB: but don't you feel that in Sudan this might be seen from a different perspective?</p> <p>5: some people will consider it and others will not</p>

Themes	Sub-themes	Illustrative quotes
		<p>14: walahi, there are people, it will depend on their level of understanding, they may not accept it.</p> <p>11: it's your responsibility, but you will face difficulties, you will face unacceptance of the idea itself I've done village work (working outside the capital city), acceptance of things like this was problematic for people. To communicate to them about family planning and to prevent circumcision of females (FGM) and things like that, we faced problems, only God knows. Our problem is our customs our society's level of awareness.</p> <p>1: depends on the people, some people consider these issues 3aib (culturally unacceptable), and other people see there is no gilat adab (disrespectful, rude) or that this person is wakiha (impolite, has no shame).</p> <p>10: like if I want to explain something to people and give them info, but I wish people would listen and accept.</p>
	Openness to health education in general and fertility specifically	<p>1: before marriage I didn't have info about sexual education (sex ed) before marriage. I felt like I didn't want to educate myself. But now I don't need a lot.</p> <p>11: it's your responsibility, but you will face difficulties, you will face unacceptance of the idea itself I've done village work (working outside the capital city), acceptance of things like this was problematic for people. To communicate to them about family planning and to prevent circumcision of females (FGM) and things like that, we faced problems, only God knows. Our problem is our customs.</p> <p>14: So the man can tell her 'everyone drinks, khawagat (westerners) drink, what happens?' (meaning nothing happens to them, they don't have fertility problems).</p> <p>11: it's your responsibility, but you will face difficulties, you will face unacceptance of the idea itself.</p>
	Implementation may be dependent on level of understanding, knowledge, education and religiosity	<p>14: walahi, there are people, it will depend on their level of understanding, they may not accept it...Not everyone will accept, everyone has a different level of understanding.</p> <p>9: some I understood and the rest I felt I needed your explanation.</p>
	Source not trusted	<p>1: depends on the people, some people consider these issues 3aib (culturally unacceptable), and other people see there is no gilat adab (disrespectful, rude) or that this person is wakiha (impolite, has no shame).</p> <p>13: it seems that it's always the case that if you trust the source (person) that the info is coming from, that's better. But if it comes from someone I don't trust, I will just leave him and go.</p>
Self-disclosure		<p>RB: do you think people will respond authentically (honestly)?</p> <p>1: no.</p> <p>11: they can convey the message, on one condition, the person has to understand the info him/herself and be convinced of it, not that he's bemasheek (just agreeing to it to my face only).</p> <p><i>Example of inconsistent answering:</i></p> <p>RB: do you have info about signs, symptoms and RFs affecting fertility?</p> <p>6: I don't have.</p> <p>RB: were you aware that these things like CSG, alcohol, smoking etc. could affect fertility? That if a spouse has an STI they can spread it to each other?</p> <p>6: yes I know.</p> <p>RB: was the info beneficial? And was there any info you were not aware of before?</p> <p>6: yes, useful, I've seen it before.</p> <p><i>Example of agreeing with interviewer:</i></p> <p>RB: so these questions didn't bother you?</p> <p>9: no.</p> <p>RB: no problem at all?</p> <p>9: no, no.</p> <p>RB: OK, do you think there is something we can do to improve this work?</p> <p>9: no, no.</p> <p>RB: so you feel this is a good or bad thing, I mean its beneficial, or its just useless? What do you think?</p> <p>9: no, no its good.</p> <p>RB: do you think you know about the signs and symptoms of delayed fertility?</p>

Themes	Sub-themes	Illustrative quotes
		<p>1: no, not a lot RB: do you have any info about the preventable risk factors for delayed fertility? 1: very little <i>Post intervention</i> RB: were you aware that these things can impact on fertility? 1: yes I'm sure (that they have an impact) RB: where you aware of this info in the past? 1: yes, especially drugs, coffee, fizzy drinks (caffeinated beverages), I know that, I have even reduced it (her consumption).</p>
	Participant generated vs endorsed	<p><i>Example of generated statement:</i> RB: what are the pros and cons of using such a questionnaire? 1: cons, there are no cons for me, the topic is normal, the pros is that it increases education (not scholastic in nature). <i>Example of endorsed statement:</i> RB: is it aadee (OK) to use this questionnaire about the educational material? 1: yes.</p>
	Influencing factors	
	Social norms	<p><i>Example of social norm of agreeability:</i> RB: so this is beneficial? 4: yes, I have benefited a lot. RB: do you think this info is important, useful? 10: Yes, useful RB: but once you were able to understand the question you had no problem answering us right? 9: yes RB: we ask 3adee (normally) there's nothing (meaning there's no problem) 2: nodding RB: so is it OK to talk about these things? 6: yes, sure RB: in society, is society able to accept something like this? 6: yes they will accept it <i>Example of social norm of communication (I share, you share)</i> RB: yes, you would read it, so do you feel you have benefited from this info? 10: yes, I have benefited, but I didn't get to know you?</p>
	Social desirability	<p><i>Examples of wanting to appear agreeable and polite:</i> RB: is there anything else you could add that you think would help us, or something to add about the info, or a specific way to talk about this topic? 1: no, your way is nice/sweet. RB: Ok would you like to know more info? 10: yes, if you will explain it to me.</p>
	Gender	<p><i>Example of male participant disagreeing with female interviewer:</i> RB: this info, did it make you think about your situation, like because of this or that, this happened to me? Did you think about your situation? 2: no I didn't think about that. <i>Example of female participant (secondary school, housewife) agreeing with female interviewer:</i> RB: do you feel like you have benefited from this? 9: yes, I have. RB: do you think others would benefit too? 9: yes, yes.</p>
	Education	<p><i>Example of confident statement by educated woman:</i> 19: OK you really have to write this in the recommendations!! RB: does it make a difference if it's a women or a man? 19: doesn't make that much difference RB: so if a man got up and gave this info to a group of girls, does that make a difference? 19: no, makes no difference RB: and if a woman got up and gave it to a group of boys? 19: yes it makes no difference because in the end she has the info. The real difference lies in whether the info is given by a specialist, not man or woman, for me personally makes no difference. 19: just like right now, if you notice, you are giving info to a man and it makes no difference, with regards to transferring the info.</p>

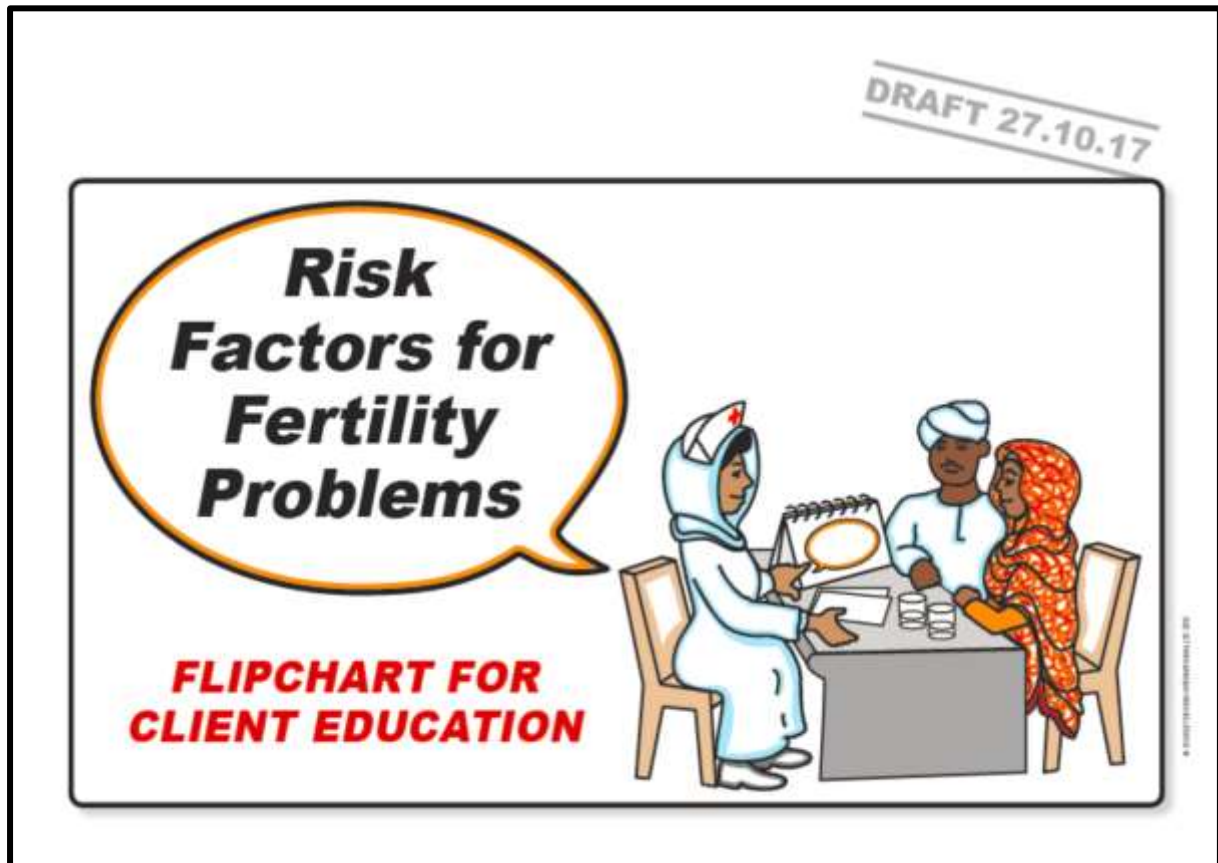
Themes	Sub-themes	Illustrative quotes
		<p>RB: but he is not a teenage boy, I'm talking about the acceptability of women giving this info to a group of teenage boys, I mean if Amel (the co-facilitator, woman about 25 years old) or I went to a boys school, teenage boys and we started to talk about sex and sexual relationships and drugs, how acceptable would this be?</p> <p>19: walahi, if you introduce yourself properly in the beginning and they see you are a doctor, a professional, a person would have their presences (the word she used 'haibtoo' suggests a dominant presence)</p> <p>When I got to the part about how important info from patients is, the wife interrupted me saying:</p> <p>19: well for example, there could be info about tight clothing, sitting for too long for boys, violent sport, nutrition has an impact</p> <p>RB: do you mean in the lifestyle?</p> <p>19: yes, there are somethings missing in the lifestyle.</p> <p>RB: so isn't it our responsibility to educate? To simplify the information?</p> <p>11: it's your responsibility, but you will face difficulties, you will face unacceptance of the idea itself.</p> <p>RB: OK, what if they found out that this issue (FGM) could affect her ability to have children?</p> <p>11: they will tell you all their mothers had children, so why will she have a problem?</p> <p>RB: what about approaching village leaders, whether they be men or women, and then they can convey the info?</p> <p>11: they can convey the message, on one condition, the person has to understand the info him/herself and be convinced of it, not that he's bemasheek (just agreeing to it to my face only).</p> <p><i>Example of uncertain response from secondary school educated housewife:</i></p> <p>RB: do you know about the signs, symptoms and risk factors for infertility? Do you have some info?</p> <p>20: no answer - looked confused.</p> <p>RB: like when to seek help? What could be a sign that there is a problem</p> <p>20: no answer - still looked confused.</p> <p>RB: would you like to know this type of info?</p> <p>20: walahi I don't know...</p>
	Age	<p>14: maybe because at that age (referring to the young women she saw), they feel embarrassed/shy to go to the doctor (for a vaginal infection).</p> <p><i>Example of older male providing rationale for his belief:</i></p> <p>RB: at what time should boys know this type of info, at what age?</p> <p>8: at puberty.</p> <p>RB: do you think a teenage boy would care/think about such things 'I will have kids in the future', or he won't be interested/care?</p> <p>8: during puberty, you are creating a human (meaning the person's personality is being formed), lots of factors, and so its possible (to give the info) after puberty (meaning after he has reached the age or puberty) he may be able to comprehend it.</p> <p>RB: so it's not a problem, for example we say 'this area, people should not talk about'?</p> <p>8: it's WRONG not to talk about it!!</p> <p>RB: so we should talk about all of this?</p> <p>8: YES, YES!!</p>
	Presence of other person	<p><i>Example: (husband and wife):</i></p> <p>19: yes it makes no difference because in the end she has the info. The real difference lies in whether the info is given by a specialist, not man or woman, for me personally makes no difference.</p> <p>18: yes, I agree, the most important thing is that they have to be a specialist.</p>
Understanding of being at risk		<p>7: Everyone knows what can harm them and can help them (meaning people can differentiate between what can harm and help them).</p> <p>And they are still doing the wrong, how, like, for example, sex, they know it can transmit diseases but they still do it. They use protection and say 'I won't get a disease'.</p> <p>They know everything but they try in different ways to do things, but this thing (premarital sex) is haram (forbidden by Islam) and wrong.</p> <p>They do it in ways and give it names. All these young people, they are aware and they know.</p>
	Universal	<p>RB: were you aware that the things we talked about could impact fertility negatively?</p> <p>3: no, [but she was pointing at the lifestyle items in the FS in my hand and nodding]</p> <p>RB: what about things like coffee and weight?</p> <p>3: yes</p>
	Age	<p>8: yes, currently (in this day and age), nowadays people are more aware, they read, the media is open (meaning western media is available), aadee (it's OK) no problem.</p>

Themes	Sub-themes	Illustrative quotes
		<p>RB: OK, so when should it be 'considered', this info, when is the best time it can be presented to the community?</p> <p>13: I imagine in high school...because this is the time of being a teenager and one has to be aware, to know.</p> <p>1: before marriage I didn't have info about sexual education (sex ed) before marriage. I felt like I didn't want to educate myself. But now I don't need a lot.</p> <p>11: the grandmothers tell us nehna min gumna (since they came to be or grew up or as far as they can remember), they have been doing this (FGM), balash kalam fareegh (stop saying nonsense).</p> <p>RB: for example, if you're 15 years old, and we told you 'if you have sex and don't use protection, later in life this could affect your ability to have a child', would you still do that, or would you change your mind? (meaning would you still have unprotected sex).</p> <p>2: yes this info is useful.</p> <p>7: The type of info I find that my nieces know, even I, I'm older, I don't know it. They are in university.</p> <p>8: during puberty, you are creating a human (meaning the person's personality is being formed), lots of factors, and so its possible (to give the info) after puberty (meaning after he has reached the age or puberty) he may be able to comprehend it.</p> <p>14: walahi, this newspaper, I see, I think people here get the news from the internet, the newspaper, just the old people, because they are used to this 'cross your legs and put on your glasses'. But in general, for people, the news info comes to them, newspapers, are not that much.</p> <p>14: maybe because at that age (referring to the young women she saw), they feel embarrassed/shy to go to the doctor (for a vaginal infection). She may take care of it herself.</p>
	Gender	<p>14: They should show this to the men too, so they don't say it's just from the woman (the fertility problem).</p> <p>17: I'm not sure why but they don't understand or don't like when a man talks (is the provider of the message), they prefer if it's a woman, not sure why, but when it's a woman they feel relaxed and can understand.</p> <p>17: yes, my sister gets up and talks, but when her male colleagues get up to talk the others tell them 'no let this girl talk, because we understand what she says better'.</p> <p>14: So the man can tell her 'everyone drinks, khawagat (westerners) drink, what happens?' (meaning nothing happens to them, they don't have fertility problems).</p>
	Previous knowledge	<p>13: but when I get a desire to know more I pick up a reference (book) or I go on the internet, certain cites, I look it up.</p> <p>1: yes, especially drugs, coffee, fizzy drinks (caffeinated beverages), I know that, I have even reduced it (her consumption).</p> <p>RB: was the info beneficial? And was there any info you were not aware of before?</p> <p>6: yes, useful, I've seen it before.</p>
	Personal experience	<p>14: For me, I mean honestly, when I went for my laparoscopy, when I came to the clinic here, I know the problem they tell you about aging, getting older, delayed marriage.</p> <p>15: walahi, every girl MUST go and get checked out before she gets married, to get herself checked, I had problems with my period, and I was not bothered with it.[I could have got treatment before, treatment time (duration of treatment) would not have been as long.</p>
	Culture (social norms, religion)	<p>11: In their understanding this (FGM) is chastity, they want their daughters this way, it's none of our (the provider whoever they are) business. We do this to our daughters.</p> <p>11: they will tell you all their mothers had children, so why will she have a problem? You brought this new thing, it wasn't there in the past.</p> <p>RB: in society, is society able to accept something like this?</p> <p>6: yes they will accept it.</p> <p>1: depends on the people, some people consider these issues 3aib (culturally unacceptable), and other people see there is no gilat adab (disrespectful, rude) or that this person is wakiha (impolite, has no shame).</p> <p>13: So, knowing about this, awareness about such things especially here in Sudan, here the girl won't go to the doctor no matter what. For example, if her period is late she should find out, if her period she could have a problem, go to the doctor.</p> <p>13: Sometimes there are people that God gives (a baby) them with someone else, it was not meant to be here (in the first marriage).</p> <p>RB: yes, exactly, this can cause STIs, which can lead to blockages internally, if untreated. These relationships (multiple unprotected) before or after marriage can cause this, these STIs can be a problem for both man and woman.</p> <p>12: anyway this is not moral.</p>

Themes	Sub-themes	Illustrative quotes
		<p>1: sex outside marriage is haram (forbidden by Islam), God has forbidden certain things because they can harm us...</p> <p>7: this thing (premarital sex) is haram (forbidden by Islam) and wrong.</p> <p>13: knowing about this, awareness about such things especially here in Sudan, here the girl won't go to the doctor no matter what. For example, if her period is late she should find out, if her period she could have a problem, go to the doctor. Here we don't have such awareness, and for us it's 3aeeb (culturally unacceptable) for an unmarried girl to go to a gynaecologist.</p> <p>13: This thing especially, boys will be boys, so you know boys can have relations (sex) as much as he wants before marriage and stuff, and then he comes and then, I mean after marriage he will have repented to God (no longer engages in sex with anyone other than his wife) and they have no problem (no extramarital affairs). The family was not paying attention to the importance of this thing, the boy can get infected with a disease, he can infect his wife in the future and that will be a bigger problem. So, seriously this thing, it has to be considered (given importance).</p>
Compatibility with worldview	About acceptability	<p>1: during puberty for sure, after entering university, after starting to mix (between the sexes), somethings should happen and somethings should not happen (behaviours).</p> <p>8: it's wrong not to talk about it.</p> <p>RB: do you think it would be beneficial to others, men, women?</p> <p>3: yes inshallah (God willing).</p> <p>13: very beneficial, they have to, they have to know it. This thing especially, boys will be boys, so you know boys can have relations (sex) as much as he wants before marriage and stuff, and then he comes and then, I mean after marriage he will have repented to God (no longer engages in sex with anyone other than his wife) and they have no problem (no extramarital affairs).</p> <p>[RB: well, we have been told that there are people in our society that will not accept this, that there are things we shouldn't say because they are unacceptable in our society. So, is it better to say or not to say?</p> <p>14: walahi, you should say it because someone will accept it and benefit, they will tell you this is right.</p> <p>RB: what is the best way to talk about this, so that it is acceptable to people? Can you describe it?</p> <p>5: a person just enters (meaning literally to enter but also figuratively to delve into a topic), this is a type of education and this is not wrong.</p>
	About self-disclosure	<p><i>Example of providing honest opinion which is consistent with her beliefs:</i></p> <p>7: And I tell you something, in this day and age, they all know, they know wrong from right. And they are doing the wrong (regardless).</p> <p>Everyone knows what can harm them and can help them (meaning people can differentiate between what can harm and help them).</p> <p>And they are still doing the wrong, how, like, for example, sex, they know it can transmit diseases but they still do it. They use protection and say 'I won't get a disease'.</p> <p>They know everything but they try in different ways to do things, but this thing (premarital sex) is haram (forbidden by Islam) and wrong.</p>
	About understanding risk	<p>13: yes, early is one year, some people wait 4 or 5 years to get tested, no I mean you have just wasted time like this. It's better that they find out, so that even if God did not will it (meaning you can't have babies), you can separate.</p> <p>13: Sometimes there are people that God gives (a baby) them with someone else, it was not meant to be here (in the first marriage).</p>
Cultural tailoring	Level of understanding or education	<p>RB: OK, so do you think this info should be known before or after marriage?</p> <p>11: that would depend on the educational level of the society. The problem with our society is that there are too few people who are educated and aware</p> <p>RB: What about the questions we asked you, were they all easy to understand or did you feel like you needed extra explaining?</p> <p>9: some I understood and the rest I felt I needed your explanation.</p> <p>RB: Ok so if we want to use this, to ask a lot of women, can we ask as is or do you think we should have the extra explanations?</p> <p>9: yes, explain</p> <p>RB: so not a lot, ok would you like to know more info?</p> <p>10: yes, if you will explain it to me</p> <p>11: By the way for older people who don't know (fertility education/awareness), the simple (meaning uneducated) people, for example there are people who go to 'khalawi' (place where people are taught the Quran), or to the 'shaikhat' (a woman religious scholar) who teach Quran.]</p>
	Gender	<p>RB: Ok, so is it better from a woman or a man?</p> <p>10: it's better from a woman of course.</p>

Themes	Sub-themes	Illustrative quotes
		<p>RB: so it's better if a woman comes and talks to the girls and she can tell them and show them?</p> <p>10: why not...a man, for example, I can't ask him questions, but you are a woman like me so I can ask you questions.</p> <p>RB: would printed materials be better or in the form of a lecture/seminar?</p> <p>17: They like it as a seminar, with men and women together, the girls always like to talk. I'm not sure why but they don't understand or don't like when a man talks (is the provider of the message), they prefer if it's a woman, not sure why, but when it's a woman they feel relaxed and can understand.</p> <p>RB: so they can ask questions</p> <p>12: yes, a specific place where they can ask, women's questions, what's happening to you. And they can give her the info she is lacking.</p> <p>RB: would printed materials be better or in the form of a lecture/seminar?</p> <p>17: They like it as a seminar, with men and women together, the girls always like to talk. I'm not sure why but they don't understand or don't like when a man talks (is the provider of the message), they prefer if it's a woman, not sure why, but when it's a woman they feel relaxed and can understand.</p>
	Gender and age	<p>RB: how do you think this type of info should be given? Would it be better as printed materials or seminars, or?</p> <p>19: walahi something printed the boys will not read it, I'm talking about my brothers at home, from my experience, but if its lectures or seminars, or they went to the schools and universities, this way they will accept it, this way they will listen, because a boy by nature wants to hear not to read</p> <p>18: but there is something! This WhatsApp (a social media app that is very popular in Sudan and the Middle East), lately, people have really been concentrating on it, that is, if this info was on WhatsApp and Facebook they will read it but not a hardcopy.</p> <p>RB: so no hardcopy, but social media?</p> <p>18: yes that's possible</p>
	Trustworthy source	<p>RB: ok so should this info come from a doctor, a social worker, a man a woman?</p> <p>13: it seems that it's always the case that if you trust the source (person) that the info is coming from them, that's better. But if it comes from someone I don't trust, I will just leave him and go.</p> <p>RB: So, it only matters if you trust them or not?</p> <p>13: yes</p>
	Religiosity	<p>RB: so what is the best way for us to get them to answer and give us this info in a suitable way, how?</p> <p>1: via questions, from the beginning you will get a sense of whether this person is willing to accept things, or not accept. For example, this sex question, most people will say 'enough I don't want to (continue)'.</p> <p>RB: so how could we ask this question about sex?</p> <p>1: these are your questions, you will be able to decide, from the beginning of the interview, you will be able to decide, they will accept or they will not accept.</p> <p>RB: but if she is unwilling to accept, this info is important for them to know, they should know that unprotected sex with multiple partners can affect their ability to have kids in the future, it can lead to diseases that can infect the spouse, so how can I convey this info, what if I get a really shy or religious patient?</p> <p>1: the religious one, in a religious way, that sex outside marriage is haram (forbidden by Islam), God has forbidden certain things because they can harm us, you reach her at her level of understanding. Each person at their level of understanding.</p>
	Religiosity and Education	<p>RB: OK, for this info, who is the best person to convey this, the doctor, social worker, for example we tell someone at a mosque and have them tell people? Who is the best person to deliver this info?</p> <p>14: as I told you, printed materials, posters, pamphlets that can reach the mum or the aunt at home, they read it. People who can't read (illiterate) can get it at the mosque, you give the info to the imam (priest) and tell him to convey at least part of the message he will not refuse. This way the people at the mosque will know something and the mums will get the printed material.</p>

Appendix S: Adapted FertiSTAT flipchart



Flipchart Cover

DRAFT 27.10.17

Using the client education tool (instructions for the provider)

This tool can help you:

- Provide information about risk factors for fertility problems
- Provide tailored information and guidance to the client about what steps they can take to protect their future fertility potential
- Engage in open discussion with and to provide support for clients

It can be used to help clients with different needs:

- Currently trying to get pregnant
- Future wish to get pregnant

This tool has instructions for the **PROVIDER** on one side and information for the **CLIENT** on the other side

Say to client:

- *If you're planning to have children now or in the future you need to start taking care of your body right now.*
- *I will help you find out what you can do for your fertility.*
- *We can do this whether you're currently trying to get pregnant or not.*

CLIENT PAGE

PROVIDER PAGE

1A

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WELCOME



1B

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DRAFT 27.10.17

WELCOME

Using this flipchart, we can help you:

- Assess your risk for infertility
- Help you think about how lifestyle choices affect fertility
- Assist in helping you decide when/if to consult with your provider about fertility

Please tell me about:

- Yourself
- Your needs
- Your questions

We hope to provide you with privacy and confidentiality

- Greet client with warmth and respect.
- Thank client for coming.
- Point to this flipchart. Explain that it will help both you and the client.

- Invite client to talk and ask questions.
- Make clear that you want to listen. Explain that you need the client to speak opening so you can help.

- Is meeting space private?
- Explain that this meeting will be confidential: "What you say will not be told to others."

NEXT MOVE: When the client is comfortable and ready to talk, begin the questions. Go to the next page.

2A

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WELCOME

Please tell me about:

Yourself

Your needs

Your questions



We hope to provide you with privacy and confidentiality

2B

DRAFT 27.10.17

General info about fertility (getting pregnant)

- **Explain to the client how the process of conception occurs**
 - Sexual intercourse
 - Sperm-egg
 - Fertile window
(*point to calendar on their side of the flip chart*)
- **For a woman to become pregnant she has to have sex with her male partner**
- **The timing of the intercourse should be within a certain time of her monthly cycle** (*point to the wheel*)
- **A woman is most fertile on the day of ovulation and 5 days before it**
- **The day of ovulation is usually around day 14 of the cycle**
(14 days after the first day of your period)

3A

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How to get pregnant



The Menstrual Cycle
About 28 Days



3B

DRAFT 27.10.17

About trying to get pregnant

- **Ask:**
 - *How old are you? Have you been trying to get pregnant? How long? (make a note on the score sheet)*
 - B – 34 years or younger and trying for 0-12 months
 - B – Over 34 years and trying for 0-6 months
 - R – Over 34 years and trying for 6 months or more
 - R – Any age and trying for more than 12 months
- **Note:** If the client is not trying to get pregnant, chose age group and consider them trying for under 6 months in the 'About trying' section.
- If the client is not clear about her age ask probing questions like when did you finish school, to help you ascertain her age
- **Age:** explain that female fertility declines after 34 years of age (reproductive window)
- **Time trying:** explain that after 12 months trying all couples must seek medical advice

4A

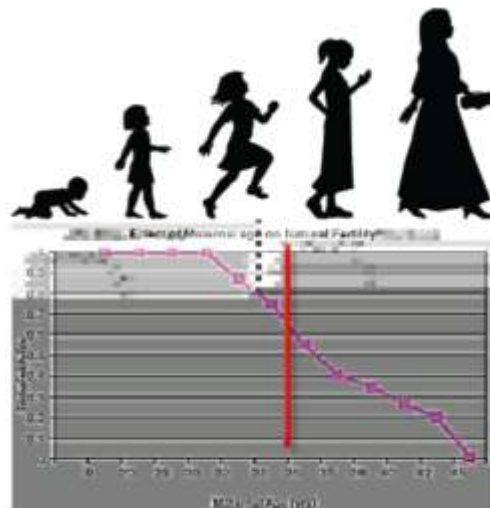
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Having children

How old are you?

Are you trying to have a baby?

How long have you been trying?



4B

DRAFT 27.10.17

Reproductive history

I want to ask you some questions about your Period:
(make a note on the score sheet)

O → Do you have severe period pains?

5A

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Is your period very painful?



5B

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Reproductive history

O → Is your period unpredictable, comes more than 5 days earlier or later than expected (not using contraception)?

If the client not sure can ask probing questions:

- What is your bleeding like?
- Do you sometimes get bleeding in between?
- What is your interval period?
- Have you always experienced this type of bleeding pattern?

(Does the client understand the menstrual cycle and what is bleeding and what isn't?)

6A

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Is your period unpredictable?



6B

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Reproductive history

- O → Does your cycle last less than 21 days (not using contraception)?**
- O → Does your cycle last more than 35 days (not using contraception)?**

If the client is not sure you can ask probing questions:

- Do you have less than 21 days between bleeding when not using a contraceptive?
- Do you have more than 35 days between bleeding when not using a contraceptive?
- How often do you menstruate when not using a contraceptive?
- Is this typical for you?

7A

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Is your cycle too short or too long?



The Menstrual Cycle
About 28 Days

7B

DRAFT 27.10.17

Reproductive history

R → Do you have a period?

Probing:

- Explore the length of time that the client has not been menstruating
- If 2-3 months, probe to see if they may be pregnant

8A

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I don't have a period



8B

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Reproductive medical history

O → Have you had pelvic surgery? (Any surgery below the naval including C-section and non-reproductive surgery).

Where were you cut and why?

9A

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Stomach Surgery



9B

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Reproductive medical history

**O → Has a doctor told you that you have endometriosis?
(explain what it is)**

O → Has a doctor told you that you have pelvic inflammatory disease (PID), now or in the past?

> Has a doctor told you that you have bacterial vaginosis (BV)?

Probing endometriosis:

- Explore the length of time that the client has not been menstruating
- If 2-3 months, probe to see if they may be pregnant

Probing PID

- Do you have pain in your lower abdomen during sex or associated with periods where you don't normally have pain.
- Do you have symptoms of PID?
 - Pain in the pelvis
 - Pain during intercourse or insertion
 - Fever
 - Vaginal discharge that smells bad
 - Irregular menstrual periods

Probing BV

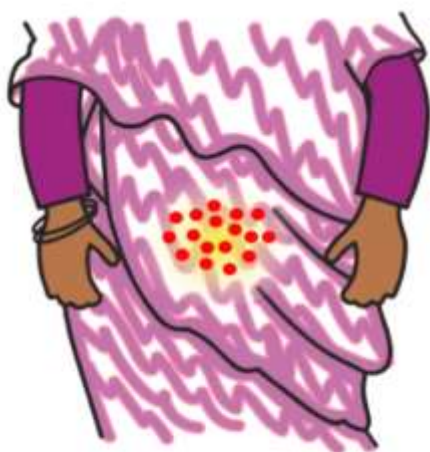
- Do you have vaginal discharge that smells bad (fishy odour)

Recommendation: try to avoid (decrease) douching, having many relationships, smoking, and using IUD

10A

DRAFT 27.10.17

Reproductive Medical History



10B

DRAFT 27.10.17

Non Communicable Diseases

Certain medical conditions and/or their treatments could potentially hinder your ability to become pregnant:

- **Diabetes:** can delay first period and lead to early menopause and can cause period problems (The reproductive period of diabetic women may be reduced due to delayed menarche and premature menopause. During the reproductive years, diabetes has been associated with menstrual abnormalities)
- **Kidney disease:** can cause less ovulation (Impaired ovulation, but once a new kidney is implanted can regain functioning)
- **Cancer:** chemo and radiation of the pelvic area cause less ovulation (accelerated depletion of ovarian reserve).
- **Thyroid Disease:** can cause period (menstrual) problems
- **Lupus:** the condition or its treatment can lead to less ovulation (Premature ovarian failure (POI), caused by autoimmune causes or drug induced)

RECOMMENDATION

If you have been told by a doctor that you have any of these conditions talk to the diagnosing physician about the side effects and impact on fertility

11 A

DRAFT 27.10.17

Medical conditions that can decrease your ability to get pregnant

**Talk to
your doctor**



11 B

DRAFT 27.10.17

Communicable Diseases

Tailor these questions to the client's level of cultural attributes (e.g. religion, modern-traditional)

- Have you had TB in the past?
- TB in the chest can lead to TB in the reproductive organs, known as GTB.
- GTB can decrease your ability to get pregnant (damage ovaries, tubes and endometrium disrupt ovulation, fertilization and implantation).
- If you have pain below the naval at times other than during your period, or you have no period, ask your doctor to check for TB.

- Have you been tested for HIV?
- Have you been counselled for HIV?
- HIV can potentially reduced ability to get pregnant

O → Has a doctor told you that you have an STI at any time?

Probing (STIs):

- I have been treated with a medicine for a vaginal infection?
- Has your sexual partner ever given you an infection in your genital area?
- If yes, how often do you get an infection
(Does the client understand the difference between an STI and a reproductive tract infection or other infections?)

RECOMMENDATIONS

GTB: if you have pain below the naval at times other than during your period or you have no period ask your doctor to : check for TB. Get regular screening for TB to help prevent GTB from developing

HIV and STIs: You should avoid barrier-free condom-less sex with multiple partners and consider getting tested for HIV if you have more than one partner, or your partner has sex with other people.

12 A

DRAFT 27.10.17

Communicable Diseases

12 B

DRAFT 27.10.17

Consanguinity (marrying a blood relative)

Are you and your partner related? (Or) Do you plan to marry a relative?

Did you have genetic counselling/testing before you got married? Or at later time?

Explain that it can potentially can increase number of pregnancies but in the long run overall fertility (number of live births is reduced)

RECOMMENDATIONS

Although marrying a close relative will not reduce the chance of getting pregnant in the long run it can lead to having fewer children, due to stillbirth and neonatal death.

Consider this before marriage and if already married to cousin (blood relative) then consider genetic testing to rule out genetic abnormalities (make referral to appropriate genetic counselling facility).

13A

DRAFT 27.10.17

Marrying a close relative

**Think
about this...**



13B

DRAFT 27.10.17

FGM

Ask if she has undergone FGM and what type (this needs probing)

Probing:

- If client says yes, ascertain type by explaining what the different types are:
- Type I, SUNNA: partial or total removal of the clitoris
- Type II, INTERMEDIATE: partial or total removal of the clitoris and labia minora ("the lips" that surround the vagina) with or without removal of the labia majora
- Type III, PHARAONIC: narrowing of the vaginal opening formed by cutting and stitching the labia minora or majora with or without removal of the clitoris
- Type IV, OTHER : all other harmful procedures to the genital for non-medical reasons

RECOMMENDATION

The severe forms of FGM are associated with a reduced chance to become pregnant due to tubal damage. FGM can also lead to labour complications which can increase morbidity and mortality of mother and child. Try to avoid FGM in future generations. If already infibulated (type III) consider deinfibulation before pregnancy and consider not having reinfibulation after giving birth (consult with local OBGYN).


14A

DRAFT 27.10.17

FGM

**Have you
undergone FGM?**

**What type
was it?**



14B

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Lifestyle

Each question in the lifestyle section should be given to the woman and then repeated with her husband (except overweight).

I want to ask you some questions about your lifestyle (daily habits):

Y ⇒ Do you smoking frequently (>10 cigarettes per day)?

Probing:

- How many (cigarettes) do they smoke per day?
- Do you smoke argela (insert local alternative for water-pipe), chew tobacco or have other smoking ways?
(DO NOT TELL THEM THAT 10 IS A LIMIT)
- If you can ascertain that the client smokes more than 10 cigarettes per day, answer YES to this question.

15A

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Smoking



15B

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Lifestyle

Y → Do you drink more than 14 units alcohol per week
(explain what that would look like)?

Tailor this question to the client's level of cultural attributes e.g. religion, modern-traditional

Probing:

- How much do they drink? (1 unit = a small glass of wine, ½ pint of beer, a single measure of a spirit).
- What do you drink (INSERT ADAPTATION OF LOCAL ALCOHOLIC BEVERAGES)
- If you can ascertain, they drink more than 14 units, answer YES to this question.

16A

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Drinking



16B

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Lifestyle

Y ⇒ Do you drink more than 7 units caffeine per day (explain what that would look like)?

Probing:

- What do you drink? Do you drink Coke? Coffee? Tea? (INSERT ADAPTATION: Local caffeine? Coffee? Tea? Energy drinks?)
- How much do you drink? (Figure out units)
- If you ascertain that they consume more than 7 units, answer yes to this question. (1 unit – a cup of coffee, ½ unit – a cup of tea or a can of soft drink such as cola)

17A

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Caffeine



17B

DRAFT 27.10.17

Lifestyle

Y → Do you smoke marijuana (Hasheesh, or local equivalent) frequently (>4 time per week)?

Tailor this question to the client's level of cultural attributes e.g religion, modern-traditional

Probing:

- Tailor question to client's level of cultural attributes
- If client says yes, ascertain how often?
- if more than 4 times a week, answer yes to this question

18A

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Marijuana



18B

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Lifestyle

Y → Have you had barrier-free condom-less sex with multiple partners with multiple partners?

If the woman appears conservative/religious or the husband is present then instead of asking as questions can just give as advice. Having sex with multiple partners without condoms can increase risk for fertility problems. Also need to state that the risk is the same if either partner is engaging in sex with multiple partners not just the women. Tailor question to client's level of cultural attributes

Probing woman:

- Do you have sex with more than one partner? Currently or in the past?
- Do you use protection when having sex? With all partners?
- How often do you have sex with people other than your regular partner?

Probing man:

- Do you have more than one wife or partner?
- Do you have a mistress?
- Do you have sex with more than one partner? Currently or in the past?
- Do you use protection when having sex? With all partners?
- How often do you have sex with people other than your regular partner?

19A

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Other Relations



19B

DRAFT 27.10.17

Lifestyle

Y → Do you feel like you can't cope with the stress you're currently experiencing?

Probing woman:

- Are you experiencing any financial difficulties?
- Do you have any marital stress?
- How safe do you feel in your daily life?
- Explore any domestic violence or sexual abuse by partner
- Do you get the kind of support from others that you need?
- Do you fear or blame yourself for any reason which affects your sexual behaviour?
- How often do you have negative feelings such as blue mood, despair, anxiety, depression
- If yes to any then ask if they feel like they can't cope with the stress caused by the situation

Probing man:

- Are you having any troubles at work?
- Do you have any marital problems?
- Do you have any financial troubles?
- Do you have problems or are unsatisfied with your sexual life?
- Explore any domestic violence or sexual abuse by partner
- Do you get the kind of support from others that you need?
- Do you fear or blame yourself for any reason which affects your sexual behaviour?
- How often do you have negative feelings such as blue mood, despair, anxiety, depression

20A

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Coping with stress



20B

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DRAFT 27.10.17

Lifestyle (woman only)

O → Are you more than 13kg (28 lb, 2 stone) overweight?



Probing:

- Does the client have a scale?
- If a scale is available ascertain BMI using the chart on the right. If a scale is not available then try to visually ascertain if the client is more than 13 kilos overweight, if appears to be then ANSWER YES.

21A

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I'm overweight



21B

DRAFT 27.10.17

Lifestyle

R → Have you ever used class A drugs (heroin, cocaine, ecstasy)?

R → Are you currently taking anabolic steroids (for non-medical uses)?

Tailor this question to the client's level of cultural attributes e.g religion, modern-traditional

Probing:

- What local drugs have you used?

22A

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Drugs



The illustration shows a syringe with an orange plunger and a needle, positioned horizontally. Below it are three groups of drugs: a cluster of pink and white round tablets, a safety razor with a grey head and a white base, and a cluster of colorful capsules in red, blue, green, and yellow.

22B

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Husband only

**R → Do you have undescended testicles?
(if husband is present)**

R → Does your husband have undescended testicles?

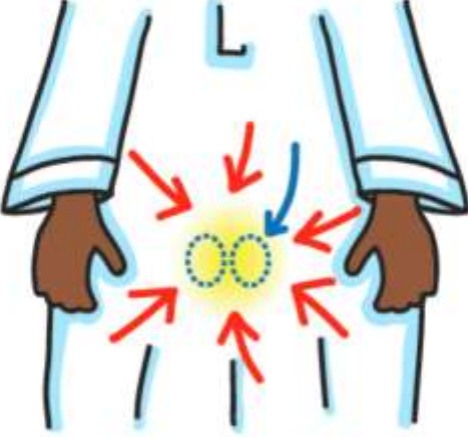
Probing:

- Have you ever had surgery on your testicles because you only have one testicle?
- When did you have your surgery?

23A

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Undescended testicles



The diagram shows a pair of hands in white lab coats holding a yellow, glowing, circular object representing a testicle. The object is positioned between the hands, which are positioned as if they are holding it. Red arrows point towards the object from the sides and bottom, while a blue arrow points towards it from the top. The object is surrounded by a dashed yellow circle.

23B

DRAFT 27.10.17

Husband only

*R → Did you get mumps any time after puberty?
(if husband is present)*

R → Did your husband get mumps any time after puberty?

Probing:

- Since his voice changed, he has had swelling in his neck and his testicles.
- Did he have swelling in his neck and testicles at the same time?

24A

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Mumps after puberty



24B

DRAFT 27.10.17

Tailored advice

Based on the score sheet give the according advice and hand over the score sheet to the client (flip client side to the appropriate guidance)

BLUE	YELLOW	ORANGE	RED
You don't have any of the risk factors but keep monitoring your situation because it may change and female fertility decreases after the age of 34 years.	You should consider changing your lifestyle habits, all these factors have an impact (can affect) on your fertility, whether or not you're trying to conceive (get pregnant). If you're not trying to get pregnant you should know that (just remember that) female fertility decreases after the age of 34 years.	These factors maybe important to your fertility. Consider seeking medical advice if you're trying to get pregnant. Your doctor may be able to give you guidance and recommend any action if needed. If you're not trying to get pregnant you should know that (just remember that) female fertility decreases after the age of 34 years.	If you're trying to get pregnant, you need to go and see your doctor for further investigation about you're situation. Drug and anabolic steroid use for non-medical reasons reduces fertility and you should consider changing these lifestyle habits, if you're not trying to get pregnant you should know that (just remember that) female fertility decreases after the age of 34 years.

25A

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What to do now



25B

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Your score was Blue

This means that:
You don't have any of the risk factors but keep monitoring your situation because it may change and female fertility decreases after the age of 34 years.

26A

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Your score was Blue

Just keep checking your status

26B

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Your score was Yellow

This means that:

You should consider changing your lifestyle habits, all these factors have an impact (can affect) on your fertility, whether or not you're trying to conceive (get pregnant). If you're not trying to get pregnant you should know that (just remember that) female fertility decreases after the age of 34 years.

27A

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Your score was Yellow

Think about changing your lifestyle habits



27B

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Your score was Orange

This means that:

These factors maybe important to your fertility. Consider seeking medical advice if you're trying to get pregnant. Your doctor may be able to give you guidance and recommend any action if needed. If you're not trying to get pregnant you should know that (just remember that) female fertility decreases after the age of 34 years.

28A

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Your score was Orange

Think about talking to a doctor



28B

DRAFT 27.10.17

Your score was Red

This means that:

If you're trying to get pregnant, you need to go and see your doctor for further investigation about your situation. Drug and anabolic steroid use for non-medical reasons reduces fertility and you should consider changing these lifestyle habits. If you're not trying to get pregnant you should know that (just remember that) female fertility decreases after the age of 34 years.

29A

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Your score was Red

If you're trying to get pregnant, you need to go and see your doctor to better understand your situation



29B

DRAFT 27.10.17

Ending: Discussion, questions & thank you

- Do you have any other questions?
- Was there something you didn't understand that you would like me to go over again?
- Are there any other issues you would like to ask me about?
- Thank you for taking the time to listen and please come back at anytime if you have more questions, want more information or support.

30A

DRAFT 27.10.17

Thank you

**Do you
have any
questions?**

**Come back
any time...**



30B

Appendix T: Adapted FertiSTAT Checklist

Checklist Tool for Signs, Symptoms and Risk Factors for Fertility Problems

Woman

How old are you? _____ years

How long have you been trying to become pregnant?
_____ years: monthsPlease indicate if any of the following reproductive health issues relate to your situation: *(tick all that apply)*

- Severe period pains
- My period is unpredictable *(can be more than 5 days early or late)*
- My period lasts less than 21 days *(no contraception)*
- My period lasts more than 35 days *(no contraception)*
- I do not have a period
- I have had surgery in my abdominal region
- I have had bacterial vaginosis *(foul-smelling discharge)*
- I suffer from endometriosis
- I have had pelvic inflammatory disease *(PID) (a serious infection in my uterus that required more than just one prescription of antibiotics)*

Please indicate if you have been diagnosed with any of the following medical conditions, infections or diseases: *(circle all that apply)*

- Non-Communicable Diseases (Diabetes, Cancer, Kidney disease, Sickle cell anaemia, Thyroid disease, Lupus)
- Communicable Diseases (Tuberculosis, Genital tuberculosis, HIV or HIV/AIDS, STIs)

Please indicate if these practices or rituals apply to your situation: *(tick all that apply)*

- I have been cut *(Female genital cutting)*
- I am married to a blood relative

Please indicate if your lifestyle includes any of the following situations: *(tick all that apply)*

- I smoke frequently *(>10 cigarettes per day) (water-pipe, chewing tobacco)*
- I can't cope with stress I'm currently experiencing
- I drink >14 units alcohol per week *(14 glasses of wine, 28 beers (1/2 pint) or 14 shots of spirit)*
- I drink >7 units caffeine per day *(7 cups of coffee or 14 cups of tea or 14 sodas)*
- I smoke marijuana frequently *(>4 times per week)*
- I'm more than 13kg (28 lb) overweight
- I have unprotected sex with multiple partners
- I have used a class A drugs in the past *(heroin, cocaine, ecstasy)*
- I'm currently taking anabolic steroids *(for non-medical uses)*

Man

How old are you? _____ years

How long have you been trying with your partner to become pregnant? _____ years: months

Please indicate if any of the following issues relate to your situation: *(tick all that apply)*

- I had the "mumps" as a child *(before puberty)*
- I have an undescended testicle
- I am married to a blood relative

Please indicate if you have been diagnosed with any of the following medical conditions, infections or diseases: *(circle all that apply)*

- Non-Communicable Diseases (Diabetes, Cancer, Kidney disease, Sickle cell anaemia, Thyroid disease, Lupus)
- Communicable Diseases (Tuberculosis, Genital tuberculosis, HIV or HIV/AIDS, STIs)

Please indicate if your lifestyle includes any of the following situations: *(tick all that apply)*

- I smoke frequently *(>10 cigarettes per day) (water-pipe, chewing tobacco)*
- I can't cope with stress I'm currently experiencing
- I drink >14 units alcohol per week *(14 glasses of wine, 28 beers (1/2 pint) or 14 shots of spirit)*
- I drink >7 units caffeine per day *(7 cups of coffee or 14 cups of tea or 14 sodas)*
- I smoke marijuana frequently *(>4 times per week)*
- I have unprotected sex with multiple partners
- I have used a class A drugs in the past *(heroin, cocaine, ecstasy)*
- I'm currently taking anabolic steroids *(for non-medical uses)*

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