Female subfertility

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Abstract

Subfertility is common, and affects one in six couples, half of whom lack an explanation for their delay in conceiving. Developments in the diagnosis and treatment of subfertility over the past 50 years have been truly remarkable. Indeed, current generations of couples with subfertility are more fortunate than previous generations as they have many more opportunities to become parents. The timely access to effective treatment for subfertility is important, as many couples have a narrow window of opportunity before the age-related effects of subfertility limit the likelihood of success. Assisted reproduction can overcome the barriers to fertility caused by tubal disease and low sperm counts, but little progress has been made in reducing the effect of increasing age on ovarian function. The next 5-10 years will likely see further increases in birth rates in women with subfertility, greater awareness of lifestyle factors and possible refinement of current assisted reproduction techniques and development of new ones. Such progress will bring challenging questions regarding the potential benefits and harms of treatments involving germ-cell manipulation, artificial gametes, genetic screening of embryos, and gene editing of embryos. We hope to see a major increase in fertility awareness, access to safe and cost-effective fertility care in low-income countries, and a reduction in the current disparity of access to fertility care.

Author contributions
Introduction (C.F.); Epidemiology (S.B., M.S.K.); Mechanisms/pathophysiology (S.R., S.M.); Diagnosis, screening and prevention (S.B., M.S.K.); Management (C.F., J.M.); Quality of life (J.B.); Outlook (C.F., S.R., J.B., J.M., S.M.); overview of the Primer (C.F.).

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J.B. has received funding from Merck Norway (Merck AB NUF) for the Norwegian translation of the Fertility Quality of Life (FertiQoL) tool and funding from Ferring International Center S.A. for the Czech translation of the FertiQoL scale. J.B. has also collaborated on an exploratory trial evaluating the benefits of a coping intervention on treatment discontinuation that was funded by Merck/Schering-Plough Pharmaceuticals. J.B. and her employer (Cardiff University) could one day receive royalties from the commercial use of Fertility Quality of Life (FertiQoL). J.B. has received speaker and consultancy fees to present on the psychological impact of infertility from Merck/Schering-Plough Pharmaceuticals, Merck KGaA, Actavis Generics, and IBSA Institut Biochimique. All other authors declare no competing interests.

[H1] Introduction

Subfertility (also commonly referred to as infertility) is defined as "a disease characterised 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". A clinical pregnancy is defined as "ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy". Both of these comprehensive definitions were reached through a consensus process at the World Health Organization (WHO), and were subsequently supported by regional fertility societies and international professional societies that address fertility care and infertility [1, 2]. Primary female subfertility refers to a woman who has never achieved a clinical pregnancy, whereas secondary female subfertility refers to a woman who has previously achieved a clinical pregnancy who cannot establish a subsequent clinical pregnancy.[1,2] The definitions cited above are clinical definitions, designed for the early detection and treatment of subfertility. Other definitions are used for demographic or epidemiological purposes. For example, an alternative definition of primary subfertility is the inability to ever bear a live child, and an alternative definition of secondary subfertility is the inability to bear a live following a previous pregnancy or live birth [3, 4]

Several critical steps are in achieving unassisted pregnancy in women. Follicular development leading to oocyte release from the ovary requires a normal menstrual cycle, which is coordinated by a complex interplay of pituitary and follicle-derived hormones. After an oocyte is released, it enters the fallopian tube where it can be fertilised by spermatozoa (sperm) that have travelled through the female genital tract (Figure 1). The fertilised oocyte develops as it moves though the fallopian tube into the uterine cavity, where it implants in the endometrium. In women, subfertility can involve any of these processes, whereas in men, subfertility centres around absent or inadequate sperm production (Box 1).

Common causes of female subfertility include ovulatory dysfunction (such as ovarian insufficiency or polycystic ovary syndrome (PCOS)), damaged or blocked fallopian tubes, endometriosis and uterine fibroids. Ovarian insufficiency is a loss of function of the ovaries that reduces the chance of pregnancy in all women from ~35 years of age, but occurs prematurely in some women. Blocked or damaged fallopian tubes can cause subfertility or an increased risk of tubal pregnancy [5, 6]. Endometriosis can create an unfavourable pelvic environment, whereas uterine fibroids can impede tubal transport, cause tubal obstruction or affect embryo implantation, both of which can lead to subfertility in women. In up to 30% of couples, no identifiable cause of subfertility can be found after completion of a standard investigation protocol and tests of ovulation, tubal patency and semen analysis, among others, are normal [7]. These cases are commonly referred to as ''unexplained' subfertility in the literature; in this Primer, we retain this term for consistency with the literature, but with the proviso that 'unexplained' does not mean that subfertility has no underlying cause, rather that the cause has not been identified.

Over the last 20 years there has been a move towards evidence-based, cost effective and safer fertility treatment. In addition, there is a general recognition by clinicians that subfertility differs from many other health conditions that are diagnosed on the basis of demonstrable pathology. As a consequence, management strategies are appropriately moving away from a traditional aetiological approach towards a prognostic approach, in which the decision to treat is based on the balance between the unassisted and treatment-related chances of pregnancy. However, the physical, psychological and financial burden of treatment can be substantial. Timely access to effective treatment is important, as many couples have a narrow window of opportunity before age limits the likelihood of success.

This Primer reviews the epidemiology, pathophysiology, assessment and clinical and psychosocial management of subfertility in women and considers priorities for future research.

[H1] Epidemiology

Up to one in six couples in Western countries have subfertility [8] and is a recognised cause of psychological distress in both men and women [9]. Between 48.5 and 72.4 million couples worldwide are estimated to have subfertility [3, 10], with 10 million couples in Sub-Saharan Africa and 14 million couples in South Asia [3]. The prevalence of subfertility varies widely between studies owing to variability in the populations sampled and inconsistency in the definition of subfertility [11] and sampling methods used. Clinical definitions of subfertility that are based on lack of pregnancy after 12 months of unprotected sexual intercourse estimate a median prevalence of 9% globally [10], although demographic definitions that are based on a 5 year period of childlessness (Figure 2) estimate rates of primary infertility as ~2% and secondary infertility of ~10% [3].

Couples are typically referred for fertility investigations if they have not been able to conceive within 12 months of sexual intercourse without using contraception. Although some couples might equate their condition of subfertility with sterility, this is an oversimplification as many will subsequently conceive [12]. The definition of subfertility is prognosis-driven and is based on data demonstrating that 84% of couples not using contraception would be expected to conceive within one year and 92% within two years [13]. However, to be meaningful, a prognosis-based approach should accommodate factors other than duration of subfertility, such as female age, frequency of intercourse, semen quality and the presence of pelvic pathology that could influence the chance of conception [14]. Ideally a model would also include psychological and lifestyle factors that affect fertility either directly or indirectly [15].
Few studies have examined long term trends in subfertility. Although the demand for ART has risen steadily over the last 20-30 years [16], this trend does not seem to be accompanied by a corresponding increase in the observed prevalence of subfertility [17, 18] Some of the reasons for increase in demand for ART are expanding indications for the IVF treatment such as unexplained infertility and diminished ovarian reserve, increased access to more patient friendly IVF program and appeal of newer technologies.

[H2] Risk factors

[H3] Lifestyle factors. In observational studies, lifestyle factors such as smoking, excessive alcohol consumption and caffeine use have been associated with reduced fertility [19, 20]. A case-control study in the United Kingdom identified negative lifestyle factors significantly associated with current subfertility, including overweight (by >13 kg), unprotected sexual intercourse with multiple partners and 'stress one cannot cope with' [19]. Cigarette smoking and marijuana use were significantly associated with increased time to conceive [20]. However, prospective research is needed to confirm these cross-sectional associations. Occupations involving exposure to reproductive toxins that can affect fertility such as nitrosamines and formaldehyde should be documented [21].

[H3] Age. One of the best-known and most well-established factors that affect fertility is the age of the woman (Figure 3) [22]. This risk factor is increasingly relevant as women worldwide delay childbearing and as the age at which a woman has her first child is rising in many societies [23]. In addition, the fertility rate (that is, the total number of children that would be born to each woman if she were to live to the end of her child-bearing years), has also fallen substantially [24]. For women, the likelihood of pregnancy is stable from puberty to ~30 years of age, after which, it declines in an accelerating rate until menopause when the chance of pregnancy approaches zero [25-27].

[H1] Mechanisms/pathophysiology

Unlike many other conditions, subfertility involves two individuals (or three, in the case of donor gametes or surrogacy). An individual might experience subfertility with one partner but not with another, and with increasing age, all women have infertility secondary to the complete loss of oocytes. By contrast, men continue to produce viable sperm throughout their life.

A key concept is the chance of achieving pregnancy in a specific ovulatory cycle at any given point in time; in contrast to other species in whom chances of conceiving are close to 100% during every menstrual cycle, in humans, even at their most fertile stages of life, changes of conceiving are, at most, 30% in a menstrual cycle [28] presumably secondary to the short window of oocyte maturation in the human oocyte. Accordingly, distinguishing whether the absence of pregnancy in a single cycle is due to natural reproductive inefficiency or the result of a specific pathophysiological situation that requires treatment is often difficult. Likewise, decisions about treatment of subfertility should be made after considering the chance of establishing a pregnancy without treatment (see Management) [12]

[H2] Age and oocyte quality

Ovarian age is a strong predictor of the chance of pregnancy and reflects the number of follicles still present in the ovary. At birth, girls have ~2 million oocytes in their ovaries, of which more than half are lost before puberty. Following the onset of ovulation, a cohort of 40-500 follicles develop each month of which, usually only one (the so-called dominant follicle) releases an oocyte [29]. The other follicles degenerate, and are ultimately lost through the process of follicular atresia. The number and quality of remaining oocytes reduces with increasing age (Figure 3) [25], leading to the age-related decline in female fertility. Estimation of the number of follicles inside the ovaries (that is, ovarian reserve) is possible using

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ultrasonography to measure the antral follicle count (AFC) or by measurement of the serum anti-müllerian hormone (AMH) level [27, 30, 31].

Recruitment and maturation of follicles in the ovary is a balanced interaction between hormones released by the hypothalamus and pituitary gland (such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH)), and those released in the ovary (AMH, inhibin A and inhibin B and estradiol) [27]. As these ovarian factors are produced by the granulosa cells of the antral follicles, reduced ovarian reserve results in lower levels of these hormones. This change in turn results in higher FSH levels . These aberrant hormonal levels cause menstrual cycle irregularities and affect the quantity and quality of available oocytes.

The effect of increased age on oocyte quality and chance of pregnancy is illustrated by pregnancy outcomes in women who receive oocytes from young donors [32]; oocytes from young donors have a higher rate of subsequent pregnancy than oocytes from older donors, even if the recipient is undergoing menopause. No established intervention to prevent this age-related decline in fertility is available, except for the use of donor oocytes.

The precise mechanism by which age affects oocyte quality is unknown. One hypothesis is an accumulation of DNA damage in the oocytes over time, through environmental stressors, for example by certain food or drug residues, or by reactive oxygen species (ROS) [33, 34]. Alternatively, a first-in-first-out principle (also known as a production line principle) has been proposed, whereby high quality oocytes are primarily ovulated early in life, causing lower quality oocytes to be ovulated at later ages. This hypothesis is based the decrease in the frequency of chiasmata (the physical crossover of homologous chromosomes) in mouse oocytes with increasing maternal age [35, 36]. These reductions could also explain the increased number of aneuploidies in oocytes, embryos and other products of conception in miscarriages in older women [37-39] .

In addition, data from mouse models suggests that shortening of telomeres in oocytes is also associated with increasing age and could also cause decreased oocyte and embryo competence [40, 41]. The female germ line could also be affected by general mechanisms underlying cellular aging, such as, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, altered intercellular function, and mitochondrial dysfunction, which could contribute to subfertility [42, 43]. As previously mentioned, the age-dependent decline in oocyte quality accelerates between 35 and 40 years of age, suggesting that oocyte ageing is time limited rather than a gradual process. This finding suggests that an underlying biological threshold value or trigger is involved in oocyte ageing, for example, the number of primordial follicles dropping below a critical threshold, thereby triggering subtle physiological events, such as hormonal (such as growth hormone and androgens) changes. These hormonal changes could affect the oocytes themselves, the surrounding granulosa cells, the process of selection from the cohort of oocytes each menstrual cycle, and oocyte maturation.

Oocyte quality can also affect development of the preimplantion embryo [44] . This is supported by the increased presence of aneuploidies in oocytes of women of advanced age (Figure 3). However, this age-related increase in aneuploidies is likely to be a consequence of poor oocyte quality, rather than the cause. Oocyte quality also influences the embryonic and fetal development, as demonstrated by the increased risk of miscarriage in older women which can be reversed by the use of oocytes from young donors [46, 47].

[H2] Specific causes of subfertility

[H3] Ovulatory dysfunction. Anovulation (a failure to ovulate) is indicated by a disturbed frequency and duration of the menstrual cycle (Figure 4). Typically, the menstrual cycle is 25-35 days in duration, but some woman never menstruate (primary amenorrhea), some can menstruate but have prolonged episodes of >6 months without a period (secondary amenorrhea), or have an irregular menstrual cycle (oligomenorrhea).

Primary amenorrhea can result from the failure of normal gonadal development or be unexplained. The failure of gonad development can be idiopathic, or can be associated with a wide range of conditions, including Turner Syndrome (in individuals with a 45, XO karyotype), hypothalamic problems secondary to a spectrum of disorders (such as extremes of body weight, chronic disease such as coeliac disease, or

high stress levels). Structural anatomical conditions, including imperforate hymen and the complete absence of the genital organs owing to the failure of normal gonadal development may also present as primary amenorrhoea.

Secondary amenorrhoea and oligomenorrhea can be caused by endocrine disorders involving the hypothalamus, pituitary gland, thyroid gland, the adrenal gland and the ovary [48]. The correction of thyroid function is required before any fertility treatment commences, as disorders of thyroid function are associated with problems in fetal development [48]. Pituitary adenomas produce high levels of prolactin, which inhibits gonadotropin-releasing hormone secretion and the production of gonadotropins, which leads to suppression of ovulation. Rarely, anterior pituitary failure occurs following severe postpartum haemorrhage (known as Sheehan Syndrome) and may result in hypopituitarism with low levels of gonadotrophins, growth hormone, adrenocorticotrophin, thyroid stimulating hormone and prolactin. Replacement therapy will be necessary and when fertility is desired then ovarian stimulation with gonadotrophins can be given.

The most-common cause of anovulation associated with oligomenorrhea and amenorrhea is polycystic ovary syndrome (PCOS) [49]. The exact causes of PCOS are not known, but women with PCOS have an increased frequency of pulses of GnRH release from the hypothalamus, which increases the LH/ FSH ratio leading to higher androgen levels, hampered follicle maturation and possible anovulation [49]. Although women with PCOS have high rates of subertility compared with women without PCOS, the majority do usually conceive with or without treatment [50].

[H3] POF and POI. In some women, decreased ovarian reserve occurs prematurely and menopause is reached earlier, in some cases when women are teenagers, which is referred to as premature ovarian failure (POF) or primary ovarian insufficiency (POI).
Causes of POF and POI include a low initial number of ovarian follicles,which can be idiopathic, or an abnormally high rate of follicular atresia (for example, Turner syndrome or fragile X syndrome) or can be caused by cytotoxic therapies. Some women with POI have a sufficient number of follicles but have specific genetic defects, enzyme deficiencies or specific autoimmune responses that affect follicular growth and maturation. In Turner syndrome, POF or POI is due to the accelerated loss of oocytes from the ovaries after the 18th week of fetal life or during the postnatal period [51]. Fragile X syndrome is caused by an increase in the number of CGG trinucleotide repeats in *FMR1* (encoding fragile X mental retardation 1 protein) [52]. Women with too many or too few CGG repeats in *FMR1* have an increased risk of menstrual cycle disturbances, POF, non-identical twinning and possibly increased rates of aneuploidy and miscarriage [52].

[H3] Ovarian cysts. Ovarian cysts are frequently detected because of the increased use of imaging such as ultrasonography and MRI. They range from simple cysts associated with the menstrual cycle (such as persistent follicular cysts) to cysts of endometriosis (endometriomata) or teratomas such as dermoid cysts. In women who are seeking to conceive, these cysts generally do not negatively impact on fertility unless they are large enough to distort tubal anatomy. Indications for removal of these cysts will depend on the symptoms and the benefits and harms of the surgery.

[H3] Pelvic, uterine and tubal abnormalities. Tubal abnormalities range in severity from scarring and mild adhesions (fibrous bands between organs) to complete blockage or absence of the fallopian tubes. In some cases, the fallopian tube is blocked at least at the distal end and is filled with fluid (hydrosalpinx). Tubal abnormalities can be caused by infections (such as chlamydia, gonorrhea, and tuberculosis) often transmitted sexually, that cause scarring and damage of the tubal tissue, in addition to peritoneal infection, previous surgeries, or endometriosis, and rarely, genetic defects [53]. Subfertility is common in women with HIV, and is usually associated with tubal blockage (most commonly hydrosalpinges) particularly in women with a history of induced abortions and tubal pathologies [54]. Uterine abnormalities can be caused by uterine fibroids, polyps or adenomyosis, or congenital malformations.

Endometriosis is a condition in which tissue from the lining of the uterine cavity grows outside the uterus into the peritoneal cavity . Endometriosis not only involves the fallopian tubes, but also will be present in the ovaries, and the tissue lining the pelvis which often leads to distorted and abnormal anatomy. This aberrantly located endometrial tissue is affected by the hormonal changes of the menstrual cycle, which makes it grow, thicken, and subsequently break down each cycle, which can lead to painful periods, heavy

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menstrual bleeding or bleeding between periods. In addition, endometriosis causes subfertility, as the aberrant endometrial tissue can result in scar formations and adhesions. The severity of endometriosis depends on the number, size, location, and depth of the endometrial implants outside the uterus [55-57].

Defects in the development of the Müllerian duct (which form the cervix, uterus, fallopian tubes and part of the vagina) can lead to abnormal development of these drugs and potentially subfertility. Approximately 1 in 4,500 women have Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, in which abnormal development of the Müllerian duct system results in the absence of the upper vagina, uterus and in some women, the fallopian tubes, but with intact ovaries and normal external genitalia [58]. Genes that are involved in prenatal development are causative, but differ between individuals. More-subtle defects in Müllerian duct development can lead to a unicornuate uterus (only half of the uterus with a single fallopian tube is present), a bicornuate uterus (an indentation in the fundus of the uterus, leading to an approximately heart-shaped uterus), or a septate uterus (the uterine cavity is partly partitioned by a longitudinal septum). These congenital uterine malformations are of unknown cause. Women with these uterine malformations can be asymptomatic, can be unaware of having these conditions and can have normal pregnancies. Some uterine malformations are associated with an increased risk of recurrent pregnancy loss and preterm birth, but an association with subfertility is less clear [59-62].

Other uterine abnormalities can be caused by fibroids, polyps or adenomyosis (in which endometrial tissue grows within the walls of the uterus). Although these conditions are often thought to be associated with a reduced chance of ongoing pregnancy because of miscarriage, there is no conclusive evidence that they adversely affect conception [63, 64]. Rare uterine abnormalities can be congenital anomalies that are acquired through, for example, prenatal exposure to diethylstilbestrol or following surgery such as intrauterine adhesions with a thin endometrium (known as Asherman syndrome) and reduce the likelihood of implantation and ongoing pregnancy.

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[H1] Diagnosis, screening and prevention

Few standard tests for the diagnosis of subfertility are available. Geographical variation in the uptake and availability of investigations is likely, owing to the affordability of these tests. Moreover, practice guidelines vary, as shown by recommendations on PCOS and systematic reviews of diagnostic evaluation of male infertility and of endometriosis [65-67].

[H2] Diagnosis

In countries with fertility care provision, couples are generally investigated after 12 months of unsuccessful attempts to conceive, or earlier if there is a clear clinical indication [1]. A comprehensive fertility assessment involves both partners and includes detailed history taking, clinical examination and appropriate investigations (Figure 5). The aim of this assessment is to identify underlying causes of subfertility and establish a prognosis for the couple [15, 68].

[H3] Comprehensive history. A detailed history taking should document the length of time a couple has been trying to conceive, menstrual patterns, previous pregnancies, medical and surgical factors, lifestyle and family history.

The age of menarche should be recorded, as an absence or delay in the onset of menarche could be associated with ovulatory dysfunction. Regular menstrual cycles are suggestive of ovulation, whereas irregular cycles and abnormal flow can be suggestive of hormonal, endometrial or uterine pathology. Dysmenorrhea (menstrual cramps), chronic or cyclical pelvic pain and dyspareunia (painful sexual intercourse) can indicate the presence of pelvic endometriosis, whereas pressure symptoms (for example on the bladder or other organs) can be indicative of uterine fibroids and ovarian cysts. Contraceptive history is important, as some hormonal methods (such as, combined oral contraceptives) can lead to a temporary disturbance in menstrual cyclicity [69], and a discussion of lifestyle is important, as some factors can affect fertility.

Examining the medical and/or surgical treatment history and any associated infection of women with a history of miscarriage or abortion might be useful to identify potential causes of secondary subfertility. A history of ectopic pregnancy and salpingectomy (the surgical removal of a fallopian tube) is suggestive of tubal damage, whereas amenorrhoea associated with peri-partum or post-partum haemorrhage might be

associated with either pituitary infarction or intrauterine adhesions (Asherman syndrome) due to vigorous dilatation and curettage.

In addition, the presence of co-existing or previous medical conditions should be carefully evaluated. Any symptoms and signs of breast disease should be investigated and a cervical smear history sought. A history of gonadotoxic therapy for a malignant disorder or an autoimmune condition can affect ovarian reserve [70], whereas infectious diseases such as tuberculosis or HIV can be associated with pelvic inflammatory disease and subfertility [71, 72]. Pelvic operations can result in adhesions leading to distorted pelvic anatomy, and can affect tubal function, whereas ovarian surgery, such as for endometriomas (endometriotic cysts), can compromise ovarian reserve.

As previously mentioned, fertility can be affected by disorders such as PCOS, ovarian insufficiency and endometriosis, which can be familial; the identification of these disorders might require clinical assessment and appropriate genetic counseling. In some contexts, cultural practices such as female genital mutilation and consanguinity can be associated with fertility problems [73, 74]. The occupation of both female and male partners should be documented and where relevant, risk of exposure to reproductive toxins should be assessed.

[H3] Physical examination. A general physical examination includes evaluation of body mass index (BMI), blood pressure, for thyroid enlargement and general assessment of secondary sexual characteristics and hair distribution, and is useful for the diagnosis of hyperandrogenism, endocrinopathies and uterine, pelvic and ovarian abnormalities.

Clinical signs of hyperandrogenism such as acne and hirsutism can suggest PCOS. The modified Ferriman Gallway score is used to assess hirsutism objectively and the score is interpreted in the context of the woman's ethnicity. For example, for women from South East Asia, it is suggested to use a cut-off point lower than the conventionally agreed threshold, as these women have a lower density of facial terminal hair [75]. Acanthosis nigricans, observed in women with PCOS, is characterized by hyperpigmented velvety skin patches on the back of the neck, axilla and inguinal creases [76]. Androgen-secreting tumours such as tumours of the adrenal gland or ovaries lead to more pronounced signs of androgen excess compared with PCOS , characterized by features of virilization (masculine traits, such as severe acne, deepening of voice, male pattern baldness and clitoromegaly). Demonstrable galactorrhoea (milky discharge from breast unrelated to pregnancy or breastfeeding) should trigger investigations to rule out a prolactinoma.

Surgical scars suggest the type of previous surgery and can guide decisions about future diagnostic or therapeutic procedures. Clear swelling in the lower abdomen can indicate a large fibroid or ovarian cyst, which can be confirmed using radiographic imaging. External inspection of the genitalia followed by a speculum examination should be carried out to assess the cervix and rule out the presence of infection, cervical polyps and vaginal septum or double cervix which helps identify congenital uterine abnormalities such as uterine didelphys and bicornuate uterus. A high vaginal and chlamydial swab can be obtained at the same time as speculum examination to assess for infectious diseases.

Transvaginal ultrasonography of the pelvis is an accurate way to visualize the uterus and ovaries and can identify ovarian cysts, endometriomas and hydrosalpinges, among other disorders. However, transvaginal ultrasonography should be used as an adjunct to, rather than a replacement for, bimanual pelvic examination. The latter remains the best way of assessing the position, consistency and mobility of large pelvic masses such as fibroids and ovarian cysts before surgery, whereas palpation of a retroverted fixed uterus and nodules in the pouch of Douglas (also known as the recto-uterine pouch) may be the only signs of deep infiltrating endometriosis [77].

[H3]Ovulation tests. A history of regular menstrual cycles is suggestive of satisfactory ovulation in most women although a test to confirm ovulation such as a mid luteal phase progesterone is usually recommended. [78] Many women may choose to use regular menstrual diaries or fertility tracking software or applications to track ovulation [79]. In terms of clinical tests of ovulation, serum mid luteal progesterone levels is considered the gold-standard, and is the most commonly used; the timing of this test is important, and samples should ideally be taken 7 days before the expected onset of the next menstrual period. Progesterone tracking (taking two or three samples over several days) can be helpful in women whose cycle length, although regular, can vary by a few days [80]. Other diagnostic tests to assess ovulation include ultrasonography-based monitoring of a developing follicle and detection of an LH surge by means of serial

measurements of serum or urinary LH levels. Although the detection of secretory endometrium via endometrial biopsy is suggestive of ovulation, this procedure is invasive and requires correct timing, and is, therefore, no longer recommended in contemporary practice [80].

The choice of ovulation test depends on patient preferences, and the cost and availability of resources to do these tests. Ultrasonography for the detection of ovulation relies on findings such as the detection of the collapse of a dominant follicle and has a sensitivity of 84% and a specificity of 89% for the confirmation of ovulation [81]. One of the advantages of urinary LH estimation is that this allows self-testing, and has a concordance rate of around 90 - 97% with ultrasonography-detected ovulation [82, 83].

In women with very irregular cycles, amenorrhoea or confirmed anovulation, measurement of serum levels of estradiol, FSH, LH, thyroid-stimulating hormone, testosterone and prolactin are warranted to identify the cause of anovulation. Anovulation can be classified as WHO Type I (or hypogonadotrophic hypogonadism), Type II (or normogonadotrophic) or Type III (hypergodanotrophic), based on serum gonadotrophin and estradiol levels (Table 1). PCOS is the most-frequent cause of anovulation in general, and Type II anovulation in particular, and is often associated with hyperandogenism. PCOS is defined by presence of two out of the three following features: oligo-ovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism or polycystic ovaries detected using ultrasonography, after excluding other related disorders [84]. Rarely, adrenal disorders or an androgen-producing tumour could cause ovulatory dysfunction associated with hyper-androgenism. In these cases, measures of 17-hydroxyprogesterone, serum testosterone, androstenedione and dehydroepiandrosterone levels are advised to discriminate between ovarian and adrenal causes.

[H3]Assessment of tubal patency. Tubal patency tests are used when initial tests confirm ovulation and, in male sexual partners, normal semen parameters. In women with anovulation, patency tests can be used prior to ovulation induction, or can be delayed until after three drug-induced ovulatory cycles. Tubal patency testing is generally considered unnecessary in couples who require ART to conceive either because of severe male factor infertility (for example, sperm count < 5 million/ ml) or women with advanced age because in ART the embryo is directly placed into the uterine cavity, bypassing the fallopian tubes. Women with a recent intrauterine pregnancy loss do not require tubal patency testing, unless post-miscarriage infection is indicated.

Commonly performed tubal patency tests include hysterosalpingography (HSG), hysterocontrastsalphingography (HyCoSy) and diagnostic laparoscopy with chromotubation. HSG involves the injection of water or oil-based radio opaque iodine dye through the cervix, under fluoroscopic guidance, and has a sensitivity of 53% and a specificity of 87% for tubal pathologies (46% and 95% for bilateral tubal pathologies, respectively) [85]. HSG is useful in ruling out tubal blockage, but has limited diagnostic value for other tubal pathologies, such as peritubal adhesions [86]. HyCoSy is less invasive than HSG and carries no risk of exposure to radiation, and involves the injection of a contrast fluid during a transvaginal ultrasonography to outline the uterine cavity and Fallopian tubes. HyCoSy has a sensitivity of 80% and a specificity of 84% for tubal pathology compared with laparoscopy [87]. Although diagnostic laparoscopy and chromotubation is considered the gold standard for tubal patency assessment, this procedure is invasive and expensive. Laparoscopy and chromotubation is performed under general anaesthesia, allows direct visualization of the entire pelvis and facilitates the detection of, for example, endometriosis and pelvic adhesions (Figure 6). In addition, this procedure allows for surgical interventions such as treatment of endometriosis, adhesiolysis for pelvic adhesions or cannulation for tubal blockage (see Management). Complication occur at a rate of 0.6 per 1,000 laparoscopies and major risks include anaesthetic complications as well as blood vessel and bowel injury [88].

The choice of tubal tests depends on the presence of risk factors, such as history of pelvic inflammatory disease, or clinical considerations such as BMI and previous abdominal surgery. Tubal patency tests should be scheduled immediately after menses (up to day 12) to avoid disruption of an early undetected pregnancy. These tests are invasive and are associated with risk of infection, therefore, chlamydia screening and prophylactic antibiotic administration where necessary are required.

[H3]Assessment of uterine and peritoneal factors. All women with infertility are offered a transvaginal ultrasonography (TVS) if they have symptoms suggesting underlying pathology [77]. TVS can detect uterine cavity abnormalities, fibroids and adenomyosis, allows visualization of the ovaries (to detect and assess ovarian cysts or endometriomas) and can be used to assess AFC. The accuracy of TVS for detecting

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intrauterine lesions varies from 52.6% to 77.2%, but is ~90.6% for uterine malformations [89, 90]. Saline infusion sonography (SIS, whereby saline is inserted into the uterine cavity to allow visualization of the intra cavitary pathologies) has a sensitivity of 0.88 and a specificity of 0.94 for detecting all intrauterine abnormalities [91]. MRI is superior to ultrasonography for the detection of congenital malformations of the uterus and lower genital tract and might be useful to guide management of fibroids and recto-vaginal endometriosis [66, 92].
Diagnostic hysteroscopy is the gold standard procedure for assessing the uterine cavity, and concurrent treatment can be provided for conditions such as endometrial polyps, uterine septum and intrauterine adhesions. The overall complication rate and risk of uterine perforation with diagnostic hysteroscopy is ~0.28% and 0.13%, respectively [93]. However, there is no evidence that routine hysteroscopy in women before assisted reproduction improves chances of conception [64, 94]

[H3]Tests for ovarian reserve.

Ovarian reserve tests can be used to identify women with POF, and are used to identify women at high risk of compromised ovarian function due to increased age (>35 years of age), a family history of early menopause or previous gonadotoxic therapy or ovarian surgery. Tests of ovarian reserve are essentially tests of ovarian responsiveness to exogenous stimulation and can be useful for planning the dose of ovarian stimulation in women who intend to have ART [95]. Common tests of ovarian reserve include levels of FSH, AMH and the AFC. Increased levels of serum FSH during the early follicular phase of the menstrual cycle are associated with reduced ovarian reserve. AMH is secreted by the granulosa cells of pre-antral and small antral follicles (<8 mm), and AMH levels are a more-accurate test of ovarian reserve, as it shows minimal intra and inter cycle variation [96]. However, concerns have been raised about the lack of universal standards for AMH resulting in differences in results based on alternative assays.

The number of ovarian antral follicles (measuring 2–10 mm in diameter) seen in the early follicular phase can be measured by TVS. An AFC of ≥12 or ≥20 per ovary when measured using a transvaginal transducer with frequencies of 7.5 MHz or 8 MHz, respectively, is used to define polycystic ovarian morphology [67, 84], whereas an AFC of ≤10 is suggestive of diminished ovarian reserve [97]. A low AFC (3–6 total antral follicles) is a predictor of poor response during IVF [98]. AMH levels and AFC are good predictors of ovarian response to gonadotrophin stimulation during IVF , but are poor at predicting pregnancy [99].

[H2] Screening and prevention

Prior knowledge regarding fertility, levels of anxiety, previous medical history and cultural pressures are drivers for health-seeking behaviour. In many countries, social-cultural issues, misconceptions and lack of education and/or funds act as barriers and can lead to underestimation of the burden of subfertility [100].

Educational interventions should be directed at improving knowledge of fertility health, which is currently modest. Indeed, one large international study surveyed fertility knowledge in 10,045 people from 79 countries who had been trying to conceive for an average of 2.8 years, and demonstrated an average correct score of 57% on a 13-item correct/incorrect scale of risk factors, misconceptions and basic fertility facts [101]. Women should be educated to understand the effects of increasing age on decreasing fertility and should be encouraged to check their personal reproductive risk profile [102], with fertility awareness tools to facilitate informed choices about their own fertility health [20, 103]. Tools are available to provide women with personalised fertility guidance such as FertiSTAT. However, as increased knowledge of fertility problems can be associated with increased anxiety, particularly in younger men and women, psychological approaches are also needed to alleviate possible anxiety caused by fertility information [104, 105]. In addition, the use of tools tailored to cultural contexts is important to provide education globally [106].

Tubal diseases associated with pelvic infections accounts for up to 35% of female subfertility in many parts of the world [107]. Screening, early detection and treatment of sexually transmitted diseases, particularly chlamydia and gonococcal infections, are important steps in reducing the long-term complications of these disorders, such as tubal subfertility. In addition, postpartum and post-miscarriage infections can cause tubal damage, and antibiotic prophylaxis should be considered whenever indicated to reduce the risk of infections. Genital tuberculosis continues to be a major cause of tubal and uterine factor subfertility in regions with high burden of the disease such as South and South East Asia and sub-Saharan Africa [71, 108], although the early detection and treatment of this condition helps reduce the risk of damage to reproductive organs [109].

Addressing exposure to environmental or lifestyle risk factors for subfertility could be used for prevention of this disorder. Exposure to several environmental toxins, such as dioxin, certain phthalates, pesticides and heavy metals, has been linked to subfertility [110, 111] and whenever possible, exposure to these toxins should be avoided. In terms of lifestyle factors, smoking and obesity are associated with subfertility [15]. The cessation of smoking and the optimization of body weight through health promotion initiatives involving increased awareness and availability of support are integral preventive measures for subfertility, but are not always effective. Fertility preservation is a key preventive measure in women who require chemotherapy and pelvic radiotherapy. In these women, interventions for fertility preservation include cryopreservation of oocyte or embryos, GnRH suppression and laparoscopic ovarian transposition (surgically moving ovaries out of the radiotherapy field) for those women who require pelvic irradiation. A multidisciplinary approach between the treating physician and fertility specialist is key to an effective preventive strategy.

[H1] Management

The initial management of women with subfertility requires explanation of any identified cause of subfertility, the provision of a realistic prognosis (with and without treatment), advice on management options (including non-intervention) and provision of information and support [112] (Table 2). The clinician should check that all couples are aware of the basic concepts of fertility such as timed intercourse, and should provide advice as required on lifestyle factors such as smoking, alcohol consumption and weight (Box 2).

[H2] Unexplained subfertility

[H3] Expectant management. The likelihood of unassisted pregnancy for women with unexplained subfertility can be estimated using a prognostic model, such as the Hunault model, which takes several factors into account, including female age, duration of trying to conceive, source of referral (from secondary or tertiary care), sperm motility and the occurrence of previous pregnancy regardless of outcome [113]. For couples with a good prognosis (defined by the Hunault model as ≥30% chance of spontaneous conception within 1 year), expectant management is appropriate as many couples will conceive without fertility interventions. Indeed, in a prospective cohort study, 60% of women with unexplained subfertility achieved pregnancy without treatment within five years [114]. However, prognostic models do not indicate when couples should stop expectant management in favour of active treatment. In addition, the currently available models are limited to prediction at the time of diagnosis, and cannot compare the effectiveness of different treatments at multiple points in time [115] . These models do not take account of other considerations, such as family size.

Dutch fertility guidelines recommend 6-12 months of expectant management for couples with a good prognosis of spontaneous pregnancy, as defined by the Hunault model [116]. This approach was as effective as starting medically assisted reproduction immediately, and did not compromise ongoing birth rates, in an audit of guideline adherence in 25 clinics [117]. By comparison, the 2013 NICE guidance in the United Kingdom recommend that IVF is offered to women with unexplained infertility who have not conceived after 2 years of regular unprotected sexual intercourse, which can include up to 1 year before their fertility investigations, and can be shorter in women >36 years or older [80].

If expectant management is not effective, or in women with a poor prognosis, options for active intervention include hysterosalpingography, intrauterine insemination or IVF, any of which might be the next step depending on prognostic factors, patient preference and treatment availability. All treatment options require a shared-decision making approach [118].

[H3] HSG. HSG is a routine test carried out as part of fertility work-up, but might also have a role in the treatment of subfertility. Tubal flushing with an oil-based dye increases pregnancy rates in women with normal fallopian tubes (39.7%) , compared with tubal flushing with a water-based dye (29.1%), both of which are well-tolerated [119, 120]. The mechanism of action of HSG on subfertility is not well understood but might involve altering the immunological environment in the peritoneal cavity to make it more favourable for fertility and/or it may facilitate the passage of oocytes through the fallopian tubes [121]. HSG

with lipiodol (an oil-based medium) is associated with subclinical hypothyroidism in a proportion of women and thyroid function testing is recommended before and after this procedure [122]. Whether any type of HSG is superior to expectant management in terms of the chances of conceiving naturally is unclear owing to lack of evidence.

[H3] Intrauterine insemination. Intrauterine insemination (IUI) is widely used as a relatively low-cost and minimally invasive intervention for unexplained subfertility. Spermatozoa isolated from the ejaculate are directly inserted into the uterus at the estimated time of ovulation, either during a natural menstrual cycle or after ovarian stimulation using oral medications such as clomiphene citrate and letrozole or injectable gonadotropins. However, until recently, this intervention had little supporting evidence [123]. Three randomised controlled trials (RCTs) have compared IUI to expectant management; two trials demonstrated no benefit of IUI [124, 125], although one trial demonstrated a beneficial result. However, the positive RCT differed from the other trials as it used ovarian stimulation and included women with an unfavourable prognosis and average of four years of infertility (Hunault score <30%). This trial demonstrated that three cycles of IUI are more effective than expectant management, with live birth rates of 31% and 9%, respectively [126].

Pelvic inflammatory disease (PID) is a potential complication of IUI, but the average incidence of PID in a general population of IUD users is only 1.6 events per 1,000 person years [127]. Use of oral ovarian stimulation with IUI might be associated with a small increased risk of multiple pregnancy (6%) and, rarely, of ovarian hyperstimulation syndrome (OHSS) [123]. The 2013 NICE guidance recommends against use of IUI [80]; however, few clinics use this advice [128], and some evidence suggests that IUI with ovarian stimulation is a safe and effective treatment for women with unexplained infertility who have an unfavourable prognosis for natural conception.

[H3] IVF. IVF is a fertility treatment whereby mature oocytes are collected from the ovaries, are fertilized by sperm outside the body and the resulting embryo(s) judged to have the best chance of pregnancy are introduced directly into the uterus (Figure 7). A related treatment is in vitro maturation (IVM), whereby immature oocytes are collected and are matured outside the body.

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IVF is the mainstay of treatment for women with tubal disease and men with poor sperm quality, but is also frequently used for unexplained subfertility although the evidence supporting the effectiveness of IVF in this population is scant. A Cochrane review found no conclusive evidence that IVF is more effective than expectant management or IUI with ovarian stimulation, in treatment-naive women with unexplained subfertility [129]. Five RCTs compared IVF versus IUI with ovarian stimulation. Four of these included treatment-naive women and found no evidence of a difference between the two treatments. However, one RCT in which all women were pre-treated with IUI and clomiphene demonstrated a higher live birth rate in women who proceeded straight to IVF than in women who received further pretreatment with gonadotrophins and IUI before IVF [130] Conversely, one small RCT demonstrated a benefit of IVF compared with expectant management in extensively pre-treated women, but the birth rate in the expectant management arm was very low [131]. IVF was more effective than unstimulated IUI [132, 133].

The success rates of IVF are similar regardless of the cause of subfertility. Reporting and comparing data about the outcomes of IVF is difficult owing to a lack of universally agreed way of reporting and difficulties in accounting for differences between women (for example, age and length of infertility) and in the number of embryos transferred. Data from over 144,000 embryo transfer cycles in European centres in 2013 (including women with all causes of infertility) reported a clinical pregnancy rate of 34.5% per embryo transfer [134]. Single embryos were transferred in 31% of women, whereas two embryos were transferred in 56% of women [134]. In Australia and New Zealand in 2016, 87.7% of cycles transferred one embryo and the overall clinical pregnancy rate was 33% for cycles that reached embryo transfer [135].

The treatment pathway for IVF is complex, comprising many steps and decision points; each step has alternative clinical approaches, some of which are supported by robust evidence whereas others require more research [136] (Supplementary Table 1 and Figure 7). Several factors can hinder the success of IVF or can increase the risk of adverse effects, such as smoking, obesity, hydrosalpinx, septate uterus,

endometrial polyps and sub-mucosal fibroids, and should be addressed before IVF starts. Some women do not respond well to the ovarian stimulation drugs and might be described as 'poor ovarian responders'; however there is little agreement about the definition of "poor response" or the best management strategy for these women [137, 138]. Single embryo transfer (SET) during IVF reduces the risk of multiple pregnancies, and a strategy of successive SETs achieves similar outcomes to double embryo transfer but with reduced multiple pregnancy rates [139]. Several factors are important for embryo transfer, including the use of drug regimens to increase the receptivity of the endometrium, timing of embryo transfer, type of transfer catheter and use of ultrasonography for guidance [136] . The retrieval of multiple oocytes after ovarian stimulation the cryopreservation of spare embryos and further embryo transfers, which could avert the need for repeated ovarian stimulation and oocyte retrieval. Pregnancy outcomes similar with frozen embryo transfer and fresh transfer [140].

In both unassisted pregnancy and IVF cycles, implantation is a key step in achieving pregnancy, and accordingly, is often referred to as the 'rate-limiting step' [141]. If three IVF attempts are unsuccessful, a diagnosis of repeated (or recurrent) implantation failure (RIF) is often made [142, 143]. However, some data suggest that a reliable diagnosis of RIF cannot be made after three IVF cycles, and that diagnosis is likely to be more reliable and cost-effective after six IVF cycles, especially in women with a poor prognosis and in centres with lower IVF success rates [144] Cohort data support a change to the definition of RIF, as the live birth rate associated with the 4th embryo transfer cycle was not significantly different from the rate associated with the 3rd cycle [135]. Women with RIF can be offered further investigations to establish causation, including endometrial receptivity tests, pre-implantation genetic screening, time-lapse imaging and immunological tests, but these tests can be invasive and costly.

[H2] Ovulation disorders

The first line treatment for subfertility in women with PCOS is lifestyle management. Advice can be aligned with recommendations that are applicable to the general population, such as obtaining a healthy weight, smoking cessation, omitting alcohol, performing exercise and management of mental health issues [145]. Women with ovulatory disorders who are overweight or obese can be advised to lose weight to improve menstrual regularity [146]. Indeed, in one RCT a 6-month weight loss intervention increased the rate of live births conceived within 24 months in obese women who were anovulatory but not in those who were ovulatory [147]. A post-hoc analysis demonstrated that among anovulatory women, the likelihood of having a live birth conceived within 24 months of the intervention was 40% [147].

If lifestyle management is not effective, women with anovulatory PCOS and no other subfertility factors should be offered ovulation stimulation, and should be educated about timed intercourse.. The first line ovulation induction drug is letrozole, an oral aromatase inhibitor, and is associated with higher rates of ovulation and live births than clomiphene citrate (an oral antioestrogen drug), and possibly with fewer multiple pregnancies [145, 148, 149] . If barriers to letrozole use are apparent, such as cost or unavailability, other drugs can be used, such as clomiphene citrate, with or without metformin [148, 150]. Metformin reduces insulin resistance and improves ovulation and pregnancy rates when used in combination with clomiphene citrate, in women with PCOS who do not respond to clomiphene alone [67] All women should be advised of potential complications associated with ovulation induction agents (such as multiple pregnancy). Women should also be advised if the use of such agents is off-label (though permitted) in countries where this is the case [145]. Women who have achieved regular ovulation with oral induction agents can continue this treatment for up to 12 months, as pregnancy and complication rates are acceptable for this time period [151]. However, prolonged use of ovulation induction agents should be avoided owing to low success rates [145]

A second-line treatment for women who fail to respond to oral induction agents is gonadotrophins, which are injectable drugs [152], . Administration of FSH (a type of gonadotrophin) is associated with higher live birth rates than clomiphene citrate (52% versus 41%) but is expensive and requires strict cycle monitoring due to the risk of multiple pregnancies. FSH is administered by daily subcutaneous injection in a chronic low-dose regimen [153]. The addition of IUI to gonadotrophins does not significantly improve the chance of conception in women with anovulatory PCOS [152]. Preliminary evidence suggests that metformin might increase the live birth rate in women undergoing ovulation induction with FSH, compared to use of FSH alone [154].

A surgical option for ovulation induction is laparoscopic ovarian surgery, which can be offered to women with PCOS. No difference in pregnancy rates has been demonstrated between laparoscopic ovarian surgery and FSH therapy as second line treatment for women resistant to clomiphene citrate [148]. Multiple pregnancy rates are markedly decreased following ovarian surgery compared with gonadotrophins [155] . When other ovulation induction therapies have failed, women with PCOS and anovulatory infertility can be offered IVF as a third-line treatment, in the absence of a clear indication for IVF. However, IVF is usually only necessary in women with PCOS who have other factors contributing to subfertility [145]

[H2] Fallopian tube disease

Subfertility associated with tubal adhesions may be treated surgically, ideally using laparoscopic techniques to remove adhesions and restore normal anatomy as much as possible. The surgery may be a stand-alone procedure, or may precede IVF. The safety and effectiveness of surgery for tubal subfertility is unknown, as no randomized studies have been conducted. Tubal surgery is associated with higher pregnancy rates in women with mild tubal disease than in those with severe tubal pathology [156]. Fertility may be restored in women with restored tubal patency, which might allow for more than one live birth to occur; however, these women have an increased risk of ectopic pregnancy [157].

Bilateral tubal blockage was the original indication for the use of IVF and is considered a first-line intervention for this indication. RCTs are generally considered unnecessary for women with tubal subfertility as the majority of women will have complete tubal blockage and no potential alternative treatment. Tubal surgery (such as salpingectomy or tubal occlusion) improves IVF success rates in women with hydrosalpinges, [158]; although the mechanism of action is unknown, it probably involves improvement of implantation by reducing inflammation in the genital tract.

[H3] Fibroids. The best way to treat fibroids to enhance fertility is controversial. Most clinical guidelines recommend hysteroscopic myomectomy for symptomatic fibroids International Federation of Gynecology and Obstetrics (FIGO) types 0 and 1 in women seeking to conceive, and this procedure is also recommended for asymptomatic fibroids by some guidelines [92]. However, a 2015 Cochrane review recommended that studies are needed to prove the effectiveness of this intervention [63]. A recent review suggests that the decision regarding such surgery can be guided by the location, size and number of fibroids, and by the availability of clinical expertise and equipment [159] . Research is in progress on medical therapies (such as selective progesterone receptor modulators) as an alternative or adjunct to surgery for treating fibroids in women seeking fertility, but there is no conclusive evidence in this area [159].

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[H3] Endometriosis. For women with minimal or mild endometriosis, excision of the lesions improves pregnancy rates in the 9-12 months following surgery (compared with ablation alone), and laparoscopic surgery is more effective than diagnostic laparoscopy [160]. In women with endometriosis undergoing ART, a 3 three month course of GnRH agonist improves pregnancy rates. [160] As ovarian surgery may diminish ovarian reserve, the need for surgery should be very carefully considered, especially in the case of recurrent endometriosis . There is no good evidence that medical treatment is effective [160].

[H2] POI

Approximately 5-10% of women with POI have a chance of spontaneous pregnancy, but most will require oocyte donation and IVF [161]. Oocyte donation involves a woman with good ovarian reserve allowing several of her oocytes to be aspirated, following ovarian stimulation during IVF treatment [161]. The oocytes are then fertilized and the resulting embryos transferred to the uterus of the prospective mother. Oocyte donation can also be used for women with ovarian failure following chemotherapy or pelvic radiation.

[H1] Quality of life

Quality of life (QOL) and emotional wellbeing are important considerations for the management of subfertility, and supporting women and their partners should be an integral part of fertility care. Although fertility clinic staff share this aim, they often lack the resources, such as time and know-how to do so [162]. Guidelines from the European Society for Human Reproduction & Embryology provides helpful tools for clinic staff to optimise patient support (for example, pocket guides, screening tools, patient information leaflets and patient administered interventions) [163].

The effect of subfertility and associated treatment on wellbeing has been extensively studied using self-report questionnaires about general health and fertility-specific QoL (e.g., FertiQoL [164]) and emotional distress (such as anxiety and depression). Subfertility is consistently associated with poorer QOL and higher levels of emotional distress compared with population norms and healthy or gynaecological controls (typically, women attending gynaecology services for non-fertility reasons) [165-167]. In addition, the effects of subfertility on emotional distress can persist into pregnancy; women undergoing ARTs report more anxiety about fetal viability and health than women with good fertility [168, 169], but have a similar rate of postpartum depression [170]. Longer-term adjustment to subfertility in longitudinal research (> 10 years) shows positive adjustment for most women [171].
The negative effect of subfertility on wellbeing is principally due to the unfulfilled child wish [171] but also to the presence of reproductive disease and treatment. The physical aspects of underlying disorders can be stigmatising, painful and emotionally demanding (such as hirsutism and acne in PCOS [172, 173], and severe pelvic pain and dyspareunia in endometriosis [174]), similar to components of treatment such as ovarian stimulation [175], waiting for pregnancy test results [176], and treatment failure [177]. Pre-existing psychological disorders [178] and coping through avoidance (such as by avoiding pregnant women) can amplify these effects, whereas perceived partner and social support can be attenuating [179].

Psychosocial interventions has been recommended to support women with subfertility, but consensus about their effect and evaluation has not been reached. The benefits of psychosocial interventions on pregnancy (if any) are likely indirect, via treatment uptake. This benefit has been suggested by evidence that distressed individuals undergo fewer treatments [180], and meta-analyses have demonstrated that emotional distress is not associated with the failure of a single ART cycle [181] but is associated with failure in studies with a longer follow-up period [182]. Also supportive is the finding that 22% of women discontinue treatment before achieving pregnancy [183]; the most commonly cited reason for discontinuation is the psychological and relationship burden of treatment [184].

Systematic reviews of QOL studies in individuals with infertility are limited by the fact that most of the primary studies include with women undergoing treatment who are from Western countries (in which women may be more resilient and have greater support). A review of population studies shows that clinical populations represent only ~55% of the infertile population in well-developed (Europe, USA) and less well developed (Chile, Gambia, Malawai, India) countries [10]. Danish register-based cohort studies show that women undergoing ART have a lower rate of depressive disorder [180] and relationship dissolution than age-matched population reference groups within five years of starting treatment [167, 180].Severe social effects, such as social stigma, marital instability and harassment by in-laws are more common and consistently reported in reviews of non-Western [185] than Western samples [165, 166].

[H1] Outlook

Alongside efforts to improve established ART techniques, we also support three priorities for future research, such as addressing the preventable causes of subfertility, providing support and alternatives for individuals with subfertility, and encouraging new initiatives to increase the global accessibility, affordability and acceptability of ART [186].

[H2] Subfertility in low-income settings

A lack of political interest coupled with the high cost of ART has led to a huge gulf between high-income and low-income countries in the provision of fertility treatment. In these countries, education, prevention, development of low cost interventions and provision of more equitable access to new technologies could be achieved [187].

Given the competing priorities for public funding, coupled with the severe effect of childlessness in developing countries, significant efforts should focus on prevention of subfertility [185, 188]. To this end, subfertility might be resolved in low income countries by improved education and utilisation of existing resources. However, tubal blockage is very common in some areas [107, 189], most likely secondary to the high prevalence of infectious diseases (such as genital tuberculosis and HIV), maternal sepsis, and unsafe abortion, and in these cases IVF is often the only treatment option. Despite the global expansion of fertility services over the past decade, IVF remains inaccessible in many parts of the world, particularly in sub-Saharan Africa [190]. New low-cost initiatives are needed to improve the worldwide accessibility,

affordability and acceptability of IVF and other subfertility treatments [186]. Indeed, simplified techniques are being developed to increase the global accessibility of IVF [191-193] and to provide high quality affordable centres in low-income countries that integrate subfertility care (including IVF) within family planning [190].

[H2] Improving diagnosis

Prompt diagnosis of fertility problems is another challenge. One third of women with PCOS had to wait for more than two years to reach a diagnosis, and nearly half had been seen by three or more health professionals in the process, in one international study. Timely diagnosis of PCOS is important, as this facilitates early lifestyle interventions that might prevent subsequent fertility problems [194] There has also been a call for early diagnosis of common reproductive disorders such as endometriosis [195] and uterine fibroids, [159] though few data are available regarding the benefit on fertility outcomes of earlier diagnosis followed by treatment for both conditions. Such conditions often have few or no symptoms to differentiate them, and diagnostic tests are expensive or invasive. No longitudinal studies of increased surveillance for endometriosis or uterine fibroids have been undertaken, making any recommendations about screening or earlier diagnosis difficult to support [66, 92]. Accordingly, greater investment in the research of the prevalence of these conditions and the value of earlier detection is required. In addition, investigation and treatment of non-tubal causes of infertility, such as male infertility, should not be overlooked.

[H2] Improving Prevention

Education is key to preventing subfertility in both high-income and low-income nations, and many young adults lack understanding of the potential limitations of their fertility (and its treatment) and how to optimize their chance conceiving [101, 104, 196, 197]. Indeed, one randomised controlled trial in Japan showed accelerated birth timing in 12 months following provision of fertility education compared to healthy pregnancy information in partnered individuals [198]. Given the steady increase in the median maternal age at first birth, future research should address the potential link between fertility knowledge, treatment beliefs and planning of parenthood. Public health programmes need to raise awareness of the effects on fertility of lifestyle choices, and of practices such as female genital mutilation and consanguineous marriage [106]. Increased research is required on effective ways to address lifestyle factors that affect fertility. In addition, some cases of subfertility could be averted by improved education on STI prevention and more comprehensive screening for STIs, including HIV and hepatitis [187]. Depending upon local prevalence rates, screening should include STIs, in addition to pregnancy or abortion-related infections and genital tuberculosis. There has been a call for more research into the pathogens responsible for subfertility [199].When subfertility cannot be prevented, more global effort is needed to de-stigmatize childlessness, and to support those – mainly women – who find themselves ostracized within societies where parenthood is socially mandatory [186, 200] .

[H2] ART

[H3] Current ART procedures will continue to improve. Research continues to seek improvements in ART outcomes, including better ways to assess embryo and oocyte quality, refinement and individualisation of stimulation and triggering protocols, optimizing culture media, improvements in ovary, testicular tissue, gamete, and embryo preservation, and techniques for identifying and optimising endometrial receptivity [201, 202]. Treatments are currently lacking that directly target the age-related decline in oocyte quality.

Many ART clinics around the world are currently offering "add-on" interventions including, time-lapse imaging, preimplantation genetic screening, mitochondrial DNA load measurement, and assisted hatching [203-205] that may be still in the early stages of development, lack clinical evidence of safety and effectiveness, and are often costly [205, 206]. It could be argued that encouraging women and couples to pay for untested and unproven technologies deprives them of the genuine added chance of pregnancy associated with having more cycles of conventional treatment [183]. In addition, some procedures (such as assisted hatching and preimplantation genetic screening) have been offered in routine clinical practice for more than a decade despite having have been demonstrated by RCTs as ineffective or even reducing the likelihood of pregnancy [205, 206]. Thus, it is our view that high quality evidence of the safety and effectiveness of ART interventions should precede, not follow, their introduction in routine clinical practice. Reproductive medicine will benefit from investment in proper evaluation of current and new procedures and finding out what is of true benefit to the patient.

[H3] Safety and ART. ART has several ongoing safety concerns, including the need to reduce multiple pregnancies and OHSS, and to ascertain the outcomes of gamete donation and the long term health of the mother and offspring. Despite good evidence favouring repeated SET over double embryo transfer, and despite improvement in cryopreservation techniques and evidence that frozen transfers are at least as good as fresh transfers [139], there has been slow uptake of SET in many parts of the world including China, the United States, the United Kingdom and other parts of Europe, and >15% of births following ART are still multiple (Figure 8) [207]. The UK attempted to improve the uptake of SET by providing a target of <10% for multiple pregnancies but this was abandoned in 2013 following a legal challenge [208]. Successful strategies to encourage SET uptake have been to provide sufficient funding of ART.If only one IVF cycle is funded or if IVF is self-funded, couples might be less likely to accept SET. Countries with good uptake of SET (for example, Belgium, Sweden, Australia and New Zealand) have relatively generous IVF state funding arrangements and have some of the lowest multiple pregnancy rates (≤5%) [32, 134, 207, 209]. To reduce the morbidity and mortality of multiple pregnancy rates, governments funding fertility clinics need to consider linking the provision of ART with mandatory SET for the first few cycles. The savings in neonatal, child and maternal health care would more than offset the provision of IVF [210].

OHSS — a life-threatening complication of ART — has been reducing in prevalence over the past decade, owing to a greater recognition of risk factors and improved management options. Hospital admission for OHSS is relatively rare (0.4% of stimulated cycles in European countries reporting that information in 2013) although there were three deaths in 2012 and two deaths in 2013 in the European Society of Human Reproduction and Embryology report [134]. Recommendations for further research include appropriately powered, well-conducted RCTs to support the current evidence base for interventions to prevent OHSS, including dose-finding studies and research to determine the optimal timing of interventions [211].

Increased imprinting disorders have been reported in children conceived though IVF and ICSI although there was insufficient evidence of an association between ART and methylation in other imprinted genes [212].

[H3] Better fertility studies. Long term follow up studies to measure important clinical outcomes in mothers who underwent ART and in their offspring, both in childhood and beyond, are needed [213]. With the exception of national or large longitudinal studies, most IVF monitoring stops shortly after birth [214] and in clinical trials, simple outcomes such as birthweight are rarely reported [215] and later child outcomes are mostly absent [216]. Accordingly, the development of a core outcome set for subfertility trials will improve reporting [217].

Owing to the increasing use of gamete donation and surrogacy, following the health of donors and the resulting children for physical and psychological health is important [218]. In some parts of the world, notably the United Kingdom, some states in Australia, New Zealand, Netherlands, Sweden and Finland, donors can no longer remain anonymous and must consent to the release of their identity if offspring request it when they reach 18 years of age. In other regions, no disclosure is required or disclosure is prohibited, for example in Spain. In the UK, no children have yet reached the age where they can access information themselves: this will be possible in 2023. However, donors and offspring can find each other in other ways (such as registers). Positive outcomes have been reported, resulting from donor/offspring meetings [219]. A greater understanding about these sometimes complex social issues would be welcome.

[H3] New ART approaches. Radical new approaches in ART include the use of stem cells to create oocytes or sperm, the creation of synthetic embryos, gene-editing, prolonged embryo culture, artificial gametes, and the development of an artificial uterus. Although these are exciting approaches, careful development and evaulation is crucial, as there is a risk that these techniques might progress to clinical use without sufficient attention to safety, effectiveness, and their societal and ethical implications [220]. A large Dutch cross-sectional survey of clinicians, subfertile couples and the general public found that such treatments were considered acceptable for six out of eight proposed indications, but that they required regulation, preferably by a national bioethics committee [221].

Responsible implementation of novel techniques is particulary important for reproductive medicine, as their effects can potentially affect future generations [221, 222]. The example of the widespread enthusiasm to introduce add-ons before there was evidence of their effectiveness suggests the need for

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greater investment in evaluative research. The lack of evidence-based medicine for subfertility may be in part due to strong beliefs, which are often guided by the commercial interests of pharmaceutical companies, device manufacturers and clinics. Individuals undertaking fertility treatment are often not sufficiently knowledgeable in this regard, and leaders in the field have a responsibility to provide them with effective treatments underpinned by quality research. Some individuals have recommended that fertility clinics and national and international bodies have a 'duty of care' to collect "long term data pertaining to the health of any children born as a result of their use" [205] . Furthermore, doctors and scientists who recommend an unproven procedure to their patients should provide comprehensive information about the lack of evidence on the safety of the intervention on the offspring and "that regulatory bodies should require clinical trials to ensure long-term maternal and neonatal follow-up" [205]. One issue with informed consent, is that a patient could agree to treatment with a technique of unknown effectiveness, but that the clinician still remains responsible for what he or she does [223]. Unproven procedures should only be offered within properly designed trials.

[H2] Barriers to treatment

Barriers to fertility care are evident world-wide. Women with subfertility in the United States were more likely to receive a medical subfertility evaluation if they were younger, had healthy lifestyle behaviours, a male partner with high~~ly~~ educational attainment and state-mandated insurance coverage for subfertility treatment [224]. Similarly, in the United Kingdom, only 57% of women with subfertility reported seeking any medical or professional help and those with lower incomes were less likely to have sought help [225], mirroring the global pattern of infertility medical-help-seeking among subfertile women [10]. Other studies have reported that greater affordability of ART is associated with greater ART use [226].

In addition, affordability is also a driver of the use of safer ART practices [227]. In women who receive interventions for subfertility, many choose to discontinue due to the emotional, relational and physical burden of treatment [184]. Therefore better care, organization and support for patients should be a priority. The recent report of an international commission suggests that the affordability of ART could be dramatically improved by the use of cheaper drugs for ovarian stimulation, and simpler laboratory and culture systems for IVF and embryo transfer [187] .

Box 1. Male subfertility

Male factor infertility is also a cause of subfertility. The male's contribution to fertility is limited to the production of functional spermatozoa that are capable of fertilizing the oocyte. A decrease in motility (asthenozoospermia) or abnormal morphology (teratozoospermia) of spermatozoa, in addition to the presence of a low number of spermatozoa (oligozoospermia) or the complete absence of spermatozoa in the ejaculate (azoospermia) can lower the chance of pregnancy [228].

Azoospermia can be caused by an obstruction or absence of the vas deferens (obstructive azoospermia), or reduced or absent sperm production in the testis (non-obstructive azoospermia). Most men with obstructive azoospermia and approximately half of men with non-obstructive azoospermia still have residual spermatogenesis in their testes, which allows for surgical retrieval of spermatozoa for intracytoplasmic sperm injection and subsequent genetic parenthood [229]. If no sperm are available in the testis, donor sperm can be used to establish a pregnancy. Men who have non-obstructive azoospermia and who also do not produce functional spermatozoa in their testis either have a block in meiosis (maturation arrest), a complete absence of germ cells (Sertoli-Cell only syndrome) or a combination of both. Several molecular mechanisms underlie maturation arrest, of which, deletions of small or large parts of the Y-chromosome are the most common detected cause [230]. Such deletions cause the loss of genes that are essential for sperm production. Azoospermia can also be an adverse effect of chemotherapy or local radiotherapy. In such cases, cryopreservation of ejaculated or surgically retrieved spermatozoa before chemotherapy is commonly used to preserve fertility in adult men. In prepubertal boys with cancer in whom spermatozoa cannot be cryopreserved before treatment, the surgical retrieval of testicular tissue to allow for future fertility restoration using testicular transplants or spermatogonial stem cell transplantation is currently under development [231].

Box 2. Lifestyle factors and the management of female subfertility.

The likely benefit of a weight loss programme for improving fertility in women is unclear. One systematic review of weight loss interventions for treating subfertility [232] included six randomized controlled trials (RCTs) reporting pregnancy in subfertile women, and demonstrated a higher rate of pregnancy in women who underwent a combination of reducing diet and exercise (54.8%), compared with standard care (49.9%). However, live birth rates did not differ significantly between the groups (48.9% versus 46.8%). The largest RCT in this systematic review, (which the review authors assessed as having at lowest risk of bias) included 577 women with obesity and infertility, and demonstrated that a 6-month weight loss intervention before fertility treatment did not increase rates of a vaginal birth of a healthy singleton at term within 24 months, compared with immediate IVF [147, 233]. In this trial, only 38% of participants achieved their target weight loss and 22% discontinued the intervention, and the unassisted pregnancy rate in the intervention group was 26% (versus 16% in controls), suggesting some benefit with weight reduction.

Obese and overweight women with infertility should be encouraged to lose weight, but as no compelling evidence supports the use of weight loss to improve live-birth rates in women undergoing IVF, it may be advisable to start fertility treatment earlier than previously recommended in women who fail to meet weight targets despite their best efforts [234].A healthy weight prior to starting fertility treatment not only improves pregnancy outcomes with or without assisted reproductive technologies (ART), but also reduces maternal and perinatal complications during pregnancy [234]. The long-term health of offspring is also a factor, as maternal obesity (that is, a BMI >30kg/m^2) is associated with an increased risk of premature death in adult offspring [235].

No RCTs have been carried out on the effect of on fertility outcomes of smoking cessation or abstinence from alcohol. A systematic review of preconception lifestyle advice found a single RCT, which examined the effect of advising women with subfertility to stop smoking and found no evidence that this influenced readiness to stop smoking. This RCT did not report fertility outcomes [236]. However, animal and observational studies indicate that cigarette smoking impairs all aspects of fertility in women, including ovarian function, fallopian tube function, fertilisation and implantation [237].

Figure 1. The female genital tract and factors that affect fertility. Several steps are required for conception, including the appropriate development and release of a mature oocyte from the ovaries, fertilization by spermatozoa, passage through the fallopian tubes and implantation into the uterus. Aberrant development of sperm (including low sperm count, low motility or low number of sperm with normal morphology) or oocytes(such as caused by anovulation), or the failure of the sperm to reach and fertilize the oocyte (such as due to a blockage, malformation or infection of the female or male genital tracts) prevents the generation of an embryo. The embryo can fail to develop during the preimplantation stages, implant outside of the uterus (ectopic pregnancy) or fail to implant in the uterus. A receptive uterine environment is required for proper embryo implantation and development, including appropriate biophysical conditions (such as temperature and pH) and developmental synchrony between a healthy embryo and a functionally competent endometrium, and a successful molecular dialogue between the two [238-241]. Consequently, uterine abnormalities or fibroids can finally prevent the implanted embryo to develop further. In addition, the cervix needs to be accessible, open and have the right environment to allow for passage, activation and capacitation of sperm.The position of the embryo in the genital tract during each stage of development is unknown and the timings in this figure are an estimation only.

Figure 2. The prevalence of primary infertility in 2010 **[Au: I've edited the title of this figure to reduce repetition with the legend, and to ensure that the term 'primary infertility' is used herein, as this is also used in the original paper - OK?]** **.**
These data are from women between 20 and 44 years of age with no previous live births, in 2010. A demographic definition of infertility was used in this study, which was based on childlessness after 5 years of unprotected sexual intercourse.
Adapted from [3].

Figure 3. Decline in natural fertility with increasing age.
The decline of the ovarian follicle or oocyte pool with increasing age likely dictates the onset of declining fertility, the transition from regular to irregular cycles and the onset of the menopause. Aging is associated with a logarithmic decline in the number of ovarian follicles. Simultaneous to a reduction in oocyte number with increasing age, there is a decrease in oocyte quality. In this figure, reduced oocyte quality is reflected by an increased percentage of embryos with aneuoploidies. Reproduced and adapted from de Bruin JP, te Velde ER, in Tulandi and Gosden RG (eds) Preservation of Fertility. London UK. Taylor and Francis p3, 2004 and JM Franasiak Fertil Steril. 2014 doi: 10.1016/j.fertnstert.2013.11.004 .

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Figure 4. The ovarian and menstrual cycle
Follicular stimulating hormone (FSH) is mildly raised at the start of the menstrual cycle and promotes the growth of the follicles. Luteinising hormone (LH) rises one to two days after the FSH and in a natural cycle ensures ovulation. Progesterone is released following ovulation and rises until the corpus luteum starts to degenerate, and has a role in preparing the endometrium for implantation. Estradiol is secreted by maturing follicle stimulated by gonadotrophins (FSH and LH). The very high levels at the end of the late follicular phase of menstruation are responsible for the LH surge required for ovulation to occur. Basal body temperature rises by 0.2 °C approximately 24 hours after ovulation. The endometrium changes from the proliferative under the influence of rising estradiol levels to secretory in the post ovulation luteal phase under the influence of progesterone and enables implantation. If no pregnancy occurs, then the progesterone levels fall and menstruation commences.

Figure 5. Investigations for subfertility.

The baseline investigations for subfertility consist of tests for confirming ovulation and transvaginal ultrasonography for female and semen analysis for male partner. Tubal patency tests are advised for suspected tubal diseases whereas hormonal tests (for example, serum prolactin, follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels) are advised for suspected ovulatory dysfunction. For suspected uterine abnormalities, 2D ultrasonography is the first line investigation, whereas women at risk of diminished ovarian reserve are offered ovarian reserve tests (e.g. AMH). AFC- antral follicle count; AMH- anti mullerian hormone. CAT – chlamydia antibody test; DHEAS – dehydroepiandrostendione sulphate; HSG- hysterosalphingography; HyCoSy- hysterosalphino-contrast-sonography; MRI –magnetic

resonance imaging; SIS- saline infusion sonography; TSH- Thyroid stimulating hormone; TFT – thyroid function test; TVUS – transvaginal ultrasonography.

Figure 6. Assessment of tubal patency.
Pelvic images during laparoscopy :A| normal pelvic anatomy. B| Pelvic inflammatory disease with bilateral hydrosalpinges (complete tubal blockage). C| Pelvic endometriosis with right ovarian endometrioma and adhesions. Adapted from Manual of Gynecological Laparoscopic Surgery. Authors Luca Mencaglia, Arnaud Wattiez. Edition illustrated. Publisher Endo-Press, 2006.

Figure 7. IVF procedure.

Gonadotrophins are given to stimulate the growth of ovarian follicles and gonadotrophin releasing hormone (GnRH) agonists are given to suppress the natural menstrual cycle and down-regulate the pituitary gland (step 1). GnRH antagonists are an alternative to GnRH agonists as they are not associated with hypoestrogenic adverse effects, flare-up, or a long down-regulation period and can be used at any time during the follicular phase; both regimens have similar live birth rates [242]. During the ovulation stimulation phase, regular monitoring by ultrasonography (with or without blood tests) is undertaken to assess the growth of the ovarian follicles and to avoid ovarian hyperstimulation [243]. When the follicles have reached an appropriate size, final maturation of the oocytes is induced (ovulation triggering). Human chorionic gonadotropin (hCG) is commonly used as a trigger, but can negatively affect endometrial receptivity and embryo quality, and increase rates of ovarian hyperstimulation syndrome (OHSS). An alternative, is the agonist trigger which is given if there is an increased risk of OHSS. Oocytes are collected, usually with a transvaginal ultrasonography probe for guidance, under general or local anaesthetic with sedation (step 2). Oocytes and sperm are combined in a petri dish for fertilisation (IVF) or alternatively, intracytoplasmic sperm injection (ISCI) can be used when sperm concentration and motility is low (step 3). The fertilised oocyte, now called a preimplantation embryo, is cultured for 2-6 days in vitro (step 4). From the pool of available embryos, one (on occasion, two) embryo is selected for transfer (step 5). Supernumerary embryos of good quality are cryopreserved and can be thawed and transferred one-by-one if pregnancy was not established after fresh embryo transfer or if the couple desires an additional child. Drugs such as progesterone or human chorionic gonadotropin are administered for luteal support, to improve the likelihood of implantation and pregnancy and are usually stopped at 12 weeks' gestation [244].

Figure 8. SET and birth outcomes.
The proportion of assisted reproductive technology (ART) cycles using single embryo transfer (SET) has increased since 2004 (not shown); during the same timeframe, the multiple pregnancy rate has reduced.

Table 1. WHO classification of anovulation[a]

WHO classification	Cause	Examples	Hormonal alteration
Type I	Hypothalamic-pituitary failure	Low body weight, Excessive exercise	Low levels of circulating gonadotropins and serum estradiol
Type II	Hypothalamic - pituitary – ovarian axis dysfunction	Polycystic ovarian syndrome	Normal levels of circulating gonadotropins and serum estradiol
Type III	Ovarian failure	Premature ovarian failure	High levels of circulating gonadotrophin and low levels of serum estradiol

[a] Advances in methods of fertility regulation: report of a WHO scientific group. *World Health Organization technical report series* **527**, 1 (1973)

Table 2: Options for fertility treatments [Au: references for display items need to be included in the main reference list; as all of the references in this table were included in the main list, I've managed to copy them into this table on your behalf so you don't need to do this. However, I've added a query after each reference I have added - please check them all carefully to ensure they are all correct!] THANKS! I will check when cleaning up the references next week, in case they jump around JM

Category	Unexplained infertility	Anovulation or PCOS	Tubal Factors, Endometriosis or Fibroids	Advanced age , diminished ovarian reserve and POI
Early management options	Use a locally applicable prediction model for natural conception E.g. (using Hunault model [113]) If prediction score ≥30%, then continue trying for unassisted pregnancy for up to 3yrs plus risk reduction [20] **[Au: ref OK? See Janes comment I THINK THIS IS THE WRONG REF AND THAT IT IS 113]** If prediction score <30% then consider 3 cycles of intrauterine insemination with oral ovarian stimulation [126] **[Au: ref OK?]** .	Ovulation induction with oral agents (up to 12 cycles) [151] **[Au: ref OK?]**	Fibroids • Merits of surgery are uncertain. Consider hysteroscopic myomectomy [63, 92] **[Au: refs OK?]** • More severe disease: Fertility outcomes uncertain: decide about surgery on considerations of pain rather than fertility [92] **[Au: ref OK?]** Endometriosis • Minimal disease: surgical excision of lesions [160]. **[Au: ref OK?]** • If undergoing ART, pretreat with 3 months of GnRH agonist [160]. **[Au: ref OK?]**	N/A
Second line early management options	N/A	• Ovulation induction with gonadotrophin [151] **[Au: ref OK?]**	N/A	N/A

Commented [JB9]: Reference 9 was a linked recommendation when advised to continue trying for unassisted pregnancy. The recommendation is that couples should identify and address lifestyle behaviours that compromise fertility

		• Laparoscopic ovarian drilling for women who do not ovulate at maximum daily dose of clomiphene citrate [155] **[Au: ref OK?]**		
Assisted Reproduction	IVF	IVF (third-line) [145] **[Au: ref OK?]**	IVF with and without GnRH analogues	• Advanced age or diminished ovarian reserve : IVF • POI : Oocyte or embryo donation [161] **[Au: ref OK?]**

GnRH, gonadotropin-releasing hormone; IVF; in-vitro fertilization; PCOS, polycystic ovarian syndrome. POI, primary ovarian insufficiency; WES World Endometriosis Society EFI Endometriosis Fertility Index. (Johnson et al 2017)

Prediction model https://www.freya.nl/probability.php

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