Cost of fertility treatment and live birth outcome in women of different ages and BMI

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Running title: Cost of fertility treatment by age and BMI

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Abstract

Study question

What is the impact of different age and BMI groups on total investigation and treatment costs in women attending a secondary/tertiary care fertility clinic?

Summary answer

Women in their early to mid-30s and women with normal BMI had higher cumulative investigation and treatment costs, but also higher probability of live birth.

What is known already?

Female age and BMI have been used as criteria for rationing publically funded fertility treatments. Population based data on the costs of investigating and treating infertility are lacking.

Study design, size and duration

A retrospective cohort study of 2463 women was conducted in a single secondary/tertiary care fertility clinic in Aberdeen, Scotland from 1998-2008.

Participants/materials, setting, methods:

Participants included all women living in a defined geographical area referred from primary care to a specialised fertility clinic over an 11 year period. Women were followed up for 5 years or until live birth if this occurred sooner. Mean discounted cumulative National Health Service costs (expressed in 2010/2011 GBP) of fertility investigations, treatments (including all types of assisted reproduction) and pregnancy (including delivery episode) and neonatal admissions were calculated and summarised by age (≤30, 31-35, 36-40, >40 years) and BMI groupings (<18.50, 18.50-24.99 (normal BMI), 25.00-29.99, 30.34.99, ≥35.00 kg/m^2). Further multivariate modelling was carried out to estimate the impact of age and BMI on investigation and treatment costs and live birth outcome, adjusting for covariates predictive of the treatment pathway and live birth.

Main results and the role of chance

Of the 2463 women referred, 1258 (51.1%) had a live birth within 5 years, with 694 (55.1%) of these being natural conceptions. The live birth rate was highest among women in the youngest age group (64.3%), and lowest in those aged >40 years (13.4%). Overall live birth rates were generally lower in women with BMI >30 kg/m^2. The total costs of investigations were generally highest among women younger than 30 years (£491 in those with normal BMI), whilst treatment costs tended to be higher in 31-35 year olds (£1,840 in those with normal BMI). Multivariate modelling predicted a cost increase associated with treatment which was highest among women in the lowest BMI group (across all ages), and also highest among women aged 31-35 years. The increase in the predicted probability of live birth with exposure to treatment was consistent across age and BMI categories (~10%), except in the oldest age group where a slightly smaller increase in the probability of live birth was observed. The ratio of increased costs to the increased probability of live birth in women who were treated increased markedly in women over the age of 40 years, but tended to fall as BMI increased within all age groups.

Limitations and reason for caution

Our results, based on retrospective observational data from a single centre, have limited generalizability and are not free from clinician and clinic selection bias which can influence the choice of treatments as well as their costs.

Wider implications of the findings

Spontaneous live birth rates were particularly high in younger women with unexplained infertility, suggesting that expectant management is a reasonable option in this group. The policy of not over-investigating older women and offering early treatment where appropriate still incurred the highest costs per additional live birth associated with treatment, owing to the lower probability of treatment success. The increased additional cost for each live birth associated with treatment for women with decreasing BMI across all age groups, suggests that it may be possible to identify a more targeted approach to treatment.

Study funding/competing interest(s)

This study was partly funded by an NHS endowment grant (Grant Number 12/48) and DM by a Chief Scientist Office Postdoctoral Fellowship (Ref PDF/12/06). There are no conflicts of interest to declare.

Key words: Fertility, Live Birth, Body Mass Index, Age, Costs

Introduction

Considerations of cost-effectiveness are increasingly influential in informing treatment decisions within the National Health Service (NHS) in the UK as well as in other health care settings across the world. Results of published studies showing that women who are older and heavier are less likely to achieve a pregnancy has led to rationing of access to publicly funded fertility treatment on the basis of age and BMI (National Collaborating Centre for Women's and Children's Health 2013). In addition, pregnant women who are obese have been shown to have a higher risk of fetal anomalies (Stothard et al 2009), operative deliveries (Poobalan et al 2009) and pregnancy complications, such as diabetes and hypertension (Cedergren 2004, Bhattacharya et al 2007), all of which can increase the cost of perinatal care (Denison et al 2014). Whilst a substantial amount of data have been published on the costs of IVF (National Collaborating Centre for Women's and Children's Health 2013), the literature contains very little on the cumulative costs of all fertility treatments and investigations (including IVF). There are also few studies which have been able to describe the cost of treatment independent and treatment dependent pregnancies and live births in couples with fertility problems. In the UK, the National Institute for Health and Care Excellence (NICE 2013), which has generated cost-effectiveness models to determine the criteria required for access to NHS funded IVF treatment, acknowledges the paucity of data in this field. A Dutch group used data from the literature to inform models on the cumulative costs and outcomes of ovulation induction, intrauterine insemination (IUI) and IVF with respect to overweight and obese women (Koning et al 2010). However, to our knowledge, no previous study has used population based data to estimate the actual impact of current practice on the cumulative costs of both fertility investigations and treatment on women in different age and BMI categories. The aim of this study was to estimate the mean total health service costs of investigating and treating women with infertility living within a defined geographical area.

Methods

Following approval from the North of Scotland Research Ethics Committee (10/S0802/57) and the relevant Caldicott Guardians, fertility and maternity data were obtained on all women residing in the Aberdeen City District who attended the Aberdeen Fertility Centre (AFC) for the first time between 1998 and 2008. These two data sources were linked using unique identifiers.

The AFC is ideally placed to carry out such a study since it holds extensive electronic fertility and maternity records for all women in Aberdeen City district and has logged all fertility investigation and treatment events since 1991. Assessments and tests were performed according to evidence-based standard operating procedures of the AFC based on the NICE guidelines of management of infertility in the UK or, prior to this, Royal College Guidelines (Royal College of Obstetricians and Gynaecologists, 1998). Details of the clinical protocols used in decision making at the AFC are included in the Supplementary Data. The Aberdeen Assisted Reproduction Unit Database (ARUD) holds details on all IVF events since 1998, and the Aberdeen Maternity and Neonatal Databank (AMND) has information on all pregnancies and deliveries occurring in Aberdeen City and district since 1950 (http://www.abdn.ac.uk/amnd/). These databases have been used previously to assess the cost of IVF treatment in women in different age and BMI categories (Maheshwari et al 2009, 2010). In this study we used them to assess the costs and outcomes of all fertility investigations and treatments in a cohort of women referred from primary care to a specialised clinic.

Data were extracted on all women for a 5 year period or until the first live birth - if this occurred sooner - after an initial visit to the AFC. A 5 year period was chosen in order to factor in any waiting time between treatments and minimise loss to follow up. The AFC database provided baseline characteristics, outcomes of diagnostic tests, infertility diagnosis, and details of clomiphene citrate, gonadotrophin and intrauterine insemination (IUI) treatments. Details of IVF treatment were obtained from the ARUD. Data on on-going pregnancies, antenatal care, obstetric care and neonatal care were obtained from the AMND. The data were linked and anonymized by the University of Aberdeen data management team, using date of first attendance at the AFC clinic, date of birth, unit number, CHI (unique identification) number and partner's date of birth.

Inclusion criteria

All women residing in Aberdeen City district (identified by their post codes) and attending AFC for the first time between 1998 and 2008 were eligible for inclusion. Those living outside Aberdeen City District were excluded as some of their maternity records were not recorded within the AMND.

Outcomes

Our outcome measure, live birth, was considered to be treatment dependent if the antenatal booking date for the pregnancy was within 3 months of a treatment cycle reporting an outcome consistent with pregnancy. A live birth was considered to be treatment independent if there was no preceding treatment cycle or if the timing and/or reported outcome of the preceding treatment cycle was inconsistent with the recorded booking date for the live birth. As AFC is the only fertility centre in Aberdeen, all pregnancies in women who had no contact with AFC were deemed (in the absence of any further information) to be treatment independent (Thompson et al 2005).

Power Calculation

Approximately 500 new couples from Aberdeen and its surrounding areas are seen in the AFC each year. As 50% of them are expected to be resident in Aberdeen City District, we anticipated a sample size of approximately 2500 new couples over the study period. Assuming that the proportions of women in each BMI category were similar to those reported by our group in a previous study (Maheshwari et al, 2009), it was estimated that a sample of 2500 women would have more than 90% power to detect a difference in costs of one third of a standard deviation between the obese group (BMI >=30kg/m^2) and the normal BMI group (18.5-24.9kg/m^2).

Resource use and costs

Costs to the health service were estimated using a combination of top-down (aggregated high level) and bottom-up (detailed micro-costing) approaches. Estimates of resource use inputs required for investigations and treatments were based on a combination of patient records (for certain quantities of consumable items), centre treatment and monitoring protocols, and the opinion of AFC clinicians. Resource items considered included staff time, consumables, capital equipment, overheads and space.

The unit costs to add to the resource use data were obtained from Aberdeen Assisted Reproduction Unit expenditure records for consumables. Staff time was valued using nationally available unit costs (per hour) incorporating gross salaries, employer superannuation and national insurance contributions, allocated overheads, and costs associated with the use of building space (Curtis 2011). These incorporate the annuitized cost of the resources invested in training health professionals (Curtis 2011).

For capital equipment, an equivalent annual cost was calculated based on the purchase price and expected serviceable life span of each item, and this in turn was used to calculate an average cost per use based on estimated annual throughput. A discount rate of 3.5% was applied to capture the opportunity cost of investing in capital equipment. Discounting is performed in economic analyses to account for societal time preference so as to determine the net present value of costs in a common base year. Where use of space associated with a procedure was missing from the staff cost ready reckoner, this was estimated using a unit cost per square metre for a new build, multiplied by the area of space used and annuitized over a 25 year period. Costs calculated are presented in Supplementary tables 1-6.

For early treatment outcomes (biochemical pregnancy, ectopic pregnancy and miscarriage) the average unit costs of diagnosing and treating these events, as reported by Maheshwari et al (2010), were inflated to 2010/2011 values (Supplementary table 3). Antenatal care contacts, including clinic appointments, scans, blood tests, and hospital admissions were valued using readily available (top-down) unit costs based on financial returns data, as were neonatal admissions (ISD Scotland, http://www.isdscotland.org/Health-Topics/Finance/Costs/File-Listings-2011.asp) (Supplementary table 6).

All the costs were expressed in 2010/2011 GBP and future costs (beyond year 1) were discounted at a rate of 3.5% per annum in line with HM Treasury recommendations and NICE (2013). Total costs were estimated for each individual by multiplying the numbers of different procedures reported by the estimated unit cost for each procedure, and then summing across all procedures.

Statistical Methods

Analyses were conducted using SPSS (version 18), STATA (version 12) and SAS (version 9.3). Characteristics of the women attending the fertility centre and treatments undertaken are reported by BMI group and for women whose BMI was missing. Comparison of baseline characteristics and treatments undertaken across BMI groups (<18.5kg/m2, 18.5-24.9kg/m2, 25-29.9kg/m2, 30-34.9kg/m2 and >=35 kg/m2) were made. Pearson's chi-squared test was used to test for an association between BMI group and each of the following variables: causes of infertility, the proportion of nulliparous women, smoking status, alcohol status, and each type of fertility treatment. The mean female age was compared between the BMI groups using analysis of variance, and the Kruskall Wallis test was used to compare duration of infertility between the BMI groups. The proportion of missing data was documented and the characteristics of, and treatments given to, patients with complete data were compared to patients with missing data using similar tests as above. Clinical outcomes, mean discounted investigation costs, mean discounted treatment costs, mean discounted pregnancy, delivery and neonatal costs, number of women treated and the mean (SD) number of treatment cycles were presented by BMI and age groups (≤30 years, 31 to 35 years, 36 to 40 years, >40 years).

The impact of age and BMI on total fertility investigation and treatment costs and live birth was assessed using general linear regression. Pregnancy, delivery and neonatal costs were not included in this part of the analysis. These models were adjusted for exposure to fertility treatment (yes/no), primary versus secondary infertility, duration of infertility, year of registration and cause of infertility (including male factor, endometriosis, ovulatory, unexplained, tubal and other). With the exception of duration of infertility and year of registration, which were entered as covariates (i.e. linear effects), all predictors were fitted as factors (i.e. categorical effects). Interactions between the fertility treatment indicator and BMI category, and between the treatment indicator and age category, were also included in the model. A significant age (or BMI) treatment interaction would suggest that the effect of BMI (or age) category on cost/live birth differs between women who did and did not have treatment. Since they help to explain further variation, any significant interactions remained in the model. These models were used to predict costs and the probability of live birth by age and BMI groupings, with and without exposure to treatment. In this calculation, the results are expressed for a cohort of patients with unexplained infertility - a group where spontaneous or treatment independent pregnancies are more common than in other groups – with all other predictors held fixed at either their reference category or mean value.

The 95% confidence intervals for the predicted probabilities and costs were calculated by drawing 3000 random bootstrap samples from the dataset. For each bootstrapped sample we fitted the models predicting cost and live birth, calculated the predicted costs and probabilities of live birth, and took the values at the 2.5th and 97.5th percentile as the lower and upper confidence limit respectively.

The above analysis was conducted using only patients with complete data. A multiple imputation process was performed to impute values for all predictors with missing information. This was performed using a combination of the Monte Carlo Markov Chain method and predicted mean matching regression (Rubin, 1987). Many other variables, aside from those used in the statistical modelling, were used to inform the imputation process. These included alcohol status, smoking status, parity, and number of cycles of different fertility treatments i.e. clomiphene citrat**e**, gonadotrophin, IUI, donor insemination, fresh IVF and frozen IVF. The statistical analysis described above was performed for the imputed database.

Results

Patient and treatment characteristics

A total of 2463 women from the Aberdeen City District attended the fertility clinic at the AFC for the first time between 1998 and 2008. Of 1736 (70.5%) women whose BMI data were available, 56% had a normal BMI (i.e. 18.5-24.9kg/m^2), 25% were overweight (i.e. 25-29.9kg/m^2) and 16% were obese (≥30 kg/m^2). Table 1 shows the baseline characteristics of women in different BMI categories along with the treatments received. Women with a BMI <18.5 kg/m^2 were significantly younger than women with BMI in the normal range and women with BMI between 30 to 34.9 kg/m^2. Over half of all women with BMI ≥ 35 kg/m^2 presented with anovulatory infertility whilst more women (36%) in the normal BMI group had unexplained infertility. Fewer women with BMI over 35 kg/m^2 underwent IVF/ICSI treatment as compared to women with lower BMIs. Women with missing BMI data were significantly older (33 versus 32 years of age), had more secondary infertility (55% versus 41%), smoked more (27% versus 22%) and had a higher percentage of tubal factor infertility (26% versus 17%) compared to women with complete data (Supplementary Table 7). A significantly lower proportion had anovulatory

(14% versus 23%) and unexplained (24% versus 31%) infertility. They also had less clomifene citrate (14% versus 21%), gonadotrophin (1% versus 3%), and IVF (29% versus 34%) treatment.

Live birth outcome

Of all the women referred to AFC from primary care with a diagnosis of infertility during the study period, 1258 (51.1%) had a live birth within 5 years with 694 (55.1%) of these being treatment independent (spontaneous) conceptions. In those ≤30 years of age, 36.7% conceived spontaneously, compared to only 9.1% of women over the age of 40 years. Out of the 1211 (49.2%) women who received any treatment, 564 (46.6%) had a treatment dependent live birth while 164 (13.5%) had a subsequent spontaneous live birth. Out of the 1252 (50.8%) women who did not receive fertility treatment, 530 (42.3%) had a spontaneous live birth (Table 2). In women of all age groups, spontaneous conception rates were higher than those as a direct result of active treatment, but were not associated with BMI (Table 2).

Costs of investigation, treatment and pregnancy

Table 3 highlights the mean investigation, fertility treatment and pregnancy costs by age and BMI group. Generally, the average cost of investigations tended to decrease with age and also tended to be lower in women classified as severely obese (≥35kg/m2). The average treatment costs generally appeared highest in women with normal BMI, except in the youngest age group. Average pregnancy and neonatal costs followed a similar pattern (reflecting the higher live birth rate in women with normal BMI) but in some age groups these costs were highest among women with BMI >35 kg/m2. The total costs of investigation and treatment were highest among women who were 30 years or younger, with BMI less than 25kg/m^2.

Table 4 shows the number of women in different age and BMI groups who were investigated, along with the resulting costs. In comparison with younger women with normal BMI, fewer women who were older (> 40 years) or heavier (BMI >30kg/m^2) underwent a laparoscopy, possibly due to concern about increased surgical and anaesthetic risks. Cheaper investigations, such as blood tests (e.g. mid-luteal progesterone and other hormonal tests), were more frequent in the obese group up to the age of 40 years. With regards to fertility treatment (Table 5), fewer women in the older (and also the youngest) age groups, and in the higher BMI groups, received IVF treatment. By contrast, more women in the youngest age group (and within some age groupings the higher BMI groups) received treatment with clomifene citrate.

Relationship between costs and age and BMI groups

To further explore the relationship between costs of fertility investigation and treatment with age and BMI, we estimated these costs whilst adjusting for factors associated with the treatment pathway and treatment success. The modelling information (including the parameter estimates for the cost model) is contained in supplementary table S8. The parameter estimate for a particular factor affecting outcome is defined as the predicted increase in cost associated with a one unit increase in the value of that covariate.

The predicted costs from these adjusted analyses are presented in Table 6 for a cohort of women with unexplained infertility – a group without an absolute barrier to conception who would be expected to have a reasonable chance of treatment independent pregnancy. The results show a cost increase associated with treatment which is higher among women in the lowest BMI group (across all age groups), and also highest among women aged 31-35 years, followed by women aged 36-40 years (compared to women in the youngest and oldest age groups).

Additional cost per additional live birth associated with treatment

A similar approach also assessed the predicted probability of live birth. The live birth outcome model shows an uplift in the predicted probabilities of live birth with exposure to treatment, which is fairly consistent across age and BMI categories (~10%), except in the oldest age group where a slightly smaller increase in the probability of live birth is observed (see Table 6 and supplementary table S9).

Table 7 shows the difference in costs and the difference in the probability of live birth between treated and untreated couples with unexplained infertility across different BMI and age groups. The ratio of these two quantities represents the additional cost per additional live birth associated with fertility treatment. This ratio appears to be fairly consistent across the three youngest age groups. However, it is consistently higher in women over the age of forty than it is for women in the other age groups (across all BMI categories). For example, in women over 40 years of age with a BMI between 18.5 and 25 kg/m^2, the cost of an additional live birth with treatment was £32,785.52. For a woman aged 36 to 40 years with similar BMI, the cost of an additional live birth with treatment was £24,249.10. A surprising finding is that this ratio tends to fall as BMI increases within all age groups. Similar findings were observed for the baseline risk predicted costs and live birth probabilities (see Supplementary Table S10).

In both models the year of registration was statistically significant meaning that the costs and live birth outcomes changed over time, as one may expect. To investigate this further we split the cohort into two time periods, i.e. 1998 to 2003 and 2004 to 2008, and refitted the models for each. Generally, there was little difference between the effects of age, BMI and treatment in the two models (supplementary Tables S11 and S12). For the cost model, the interaction between age and treatment status was not statistically significant for the earlier time period but was for the latter time period, with significantly less costs for treatment in women over 40 years.

Multiple imputation of missing data (mainly BMI) did not appear to alter the magnitude and direction of the results substantially (supplementary tables S13 and S14) but the inclusion of 947 extra patients increased the statistical power resulting in narrower confidence intervals and more highly significant parameter estimates. The predicted probabilities of live birth were generally slightly higher across all the age and BMI categories than those based on the analysis on the complete data (Supplementary Table S15). The predicted costs from the analysis with imputed data were also slightly higher for all age and BMI categories apart from the lowest BMI category which had lower estimates.

Discussion

Principal findings

The results of this study show that within each age category, more women conceived spontaneously than as a result of fertility treatment. However, in women who received treatment, over 60% had a live birth either as a result of treatment (46.6%) or spontaneously at a later point in time (13.5%). Of those who did not receive treatment, 42.3% had a live birth. This explains why the increased predicted probability of live birth following treatment (versus no treatment) was higher across all age and BMI groups. The size of this increase was fairly consistent across BMI and age, although it fell substantially in women over the age of 40 years.

The cost of fertility investigations increased in line with BMI in normal BMI and overweight women, but was lower in women classified as obese (≥30kg/m2) and women >40 years. Women with normal BMI who had the highest overall conception rate incurred the highest costs of treatment as well as pregnancy and neonatal costs. In contrast, older women (> 40 years) and women in the high BMI groups were less likely to receive invasive investigations, such as laparscopy, and expensive treatments such as IVF. Total costs were highest in women aged 30 years or less with a BMI less than 18.5kg/m2. The overall probability of live birth tended to decrease with increasing BMI within each age group. The ratio of the predicted increase in costs to the predicted increase in the probability of live birth (with treatment) was consequently highest for women in the oldest age group (>40 years), but tended to decrease with increasing BMI within each age group.

Strengths and weaknesses of the study

To our knowledge, this is the first study to explore the overall cost of providing fertility services to women of different ages and BMI groups, using direct health service costs and a relatively large sample of women. Whilst 29.5% of patients had missing BMI information, inclusion of data on these women using multiple imputation produced results which were similar to those where these were excluded.

As expected, several age and BMI group combinations were under-populated (as shown in Table 2) which may have introduced a level of uncertainty in the results for these groups. However, as the tests of model fit and residual plots were satisfactory, the impact on the final quality of this analysis is likely to be small. A key drawback of this study is the single centre retrospective design which made it impossible to adjust for clinician preference bias against planning investigations and treatment in older and heavier women which may have resulted in lower costs in these groups. However, due to the dominance of the non NHS private sector in fertility care and natural bias associated with under reporting of spontaneous pregnancy outcomes, it would be difficult to replicate this study in any other setting. Aberdeen is unique in being a city with a single NHS fertility clinic (which is also the only provider of IVF in the region) and an NHS maternity unit, with no provision of either service in the private sector. The live birth rates by age group in women who underwent IVF treatment at Aberdeen Fertility Centre in 2012 (33%, <35 years; 24%, 35-37 years; 19%, 38-39 years; 6%, >40 years) (see http://www.aberdeenfertility.org.uk/success-rates/) were reasonably similar to the national average for 2011 (32.2%, <35 years; 27.4%, 35-37 years; 19.9%, 38-39 years; 13.4%, 40-42 years; 5.1%, 43-44 years; 0.8%, >44 years) (Human Fertilisation and Embryology Authority, 2013).

Strengths and weaknesses in relation to other studies

A relatively high rate of spontaneous conception in a cohort of infertile couples has been demonstrated previously, especially for unexplained infertility (Brandes 2011, Collins 1995). This finding was confirmed on a much larger population by our study which is one of very few in the literature to be able to analyse longitudinal data on a population based cohort due to the unique nature of local fertility services. Most clinic based fertility studies have a natural reporting bias in terms of not being able to follow up women who conceive without treatment, while population based surveys based on self-completion of questionnaires can suffer from recall bias in terms of details of diagnosis and treatment.

This is the first study to provide a comprehensive assessment of total NHS costs for the diagnosis, treatment and follow-on care after pregnancy in women with infertility. A previous study (Maheshwari et al, 2009) has investigated the impact of women's BMI on IVF costs but was unable to capture the total costs of fertility management. A subsequent study by Koning et al (2010) addressed the costs of fertility treatment in general for a hypothetical cohort of 1000 ovulatory and anovulatory women of different weight categories. That study did not account for other conditions, such as sperm dysfunction or tubal factor, and, in the absence of patient level data, relied on modelling techniques based on estimates published in the literature. Thus, it lacked precision and external validity due to its reliance on diverse sources of costs and outcomes reported in the literature over a long time period. In their model, Koning et al (2010) assumed that all overweight and obese women would follow the same pathway, although in actual fact, physician and patient choices can mean that this is not always the case. Studies on direct health service costs of IVF treatment in women in different age groups (Maheshwari et al 2009, Suchartwatnachai et al 2000) showed that the cost of live birth increased with age and was considerably higher in women over 40 years. This was in agreement with our findings though Suchartwatnachai et al, (2000) used charges rather than direct health service costs. Phillips et al (2000) has explored the costs of providing fertility treatment in women with different causes of infertility but none of the above mentioned studies has explored the costs of investigating infertile couples.

Meaning of the results

Higher costs in younger women with normal BMI reflect prevailing practice based on expert guidance (Balen and Anderson 2007). Unlike overweight and obese women in whom invasive tests or treatment are conditional on weight loss, younger and leaner women are more likely to be considered to be fit for full investigation and eligible for a greater number of treatments. As fertility is known to decline with age, older women are either likely to be offered rapid access to IVF or discouraged from active treatment if the prognosis is expected to be very poor. Thus, they are less likely to undergo expensive tests of tubal evaluation which are unlikely to contribute to clinical decision making, or incur the costs of IVF when the outcome is expected to be poor. In contrast, younger women may be offered a variety of treatments, such as IUI, before moving onto more definitive treatment like IVF which is often perceived as a last resort.

In terms of interpreting our results relating to costs and outcomes in older women, it is worth noting that women over 40 years were not eligible for NHS funded IVF during our study period. It is possible that our findings reflect the fact that only those deemed to have the best chance of conceiving (based on unobserved factors) decided to proceed with self-funded treatment. Younger women, who were more likely to receive NHS funded IVF had a better prognosis, but also a higher rate of multiples which contributed to increased combined pregnancy, delivery and neonatal costs. The finding that the additional cost per live birth (associated with fertility treatment) decreased with BMI within age groups could be explained by the association between BMI and certain types of infertility. For example, in comparison to women with a normal BMI, fewer women with polycystic ovary syndrome, who tend to have a higher BMI, are likely to need IVF as they can often be treated successfully with less costly alternatives such as ovulation induction.

Women with very low and very high BMI were younger at their first consultation, possibly because symptoms of anovulation, such as irregular or absent periods, prompted them to seek medical advice sooner.

Within each age category, spontaneous conception rates were higher than those associated with fertility treatment. This supports the results of recent studies which have shown that young women with unexplained infertility have a higher spontaneous conception rate and early treatment does not appear to necessarily improve their chances (Steures et al, 2006, Bhattacharya et al, 2008, Brandes et al, 2011, Kamphuis et al, 2014) in comparison with expectant management.

The additional cost per additional live birth with treatment was highest for women over 40 years of age, mainly due to the small increase in probability of treatment associated live-birth in this group.

This ratio showed a decreasing trend with rising BMI within all age groups, partly reflecting the fact that invasive and expensive investigations and treatments were more likely to be withheld in this group. Although local policy in keeping with British Fertility Society policy and practice guidelines (Balen and Anderson 2007) excluded women with BMI> 35kg/m2 from IVF treatment, some of them had spontaneous pregnancies.

As changes in practice, clinical decision-making and resource use patterns are inevitable over the 11 year study period, we fitted the models predicting costs and live birth separately for two time periods (1998 to 2003 and 2004 to 2008) as a *post hoc* analysis. We found that for the first half of the study period there were no significant differences in total investigation and treatment costs across age groups in those treated and not treated. However, during the second half, women aged 31 to 35 years who received treatment incurred significantly higher costs than those in other age groups whilst treated women over 40 years incurred significantly lower costs. This suggests that early targeted delivery of IVF treatment to older women with a better prognosis may have become more frequent in more recent years.

Implications for clinicians and policy makers

The fact that treatment independent conception rates were higher than those associated with active treatment in the different age groups and predictably highest in younger women with unexplained infertility suggests that expectant management is a reasonable option in this group. However, it should be noted that the presence of other unmeasured patient and clinician factors may mean that for some of these patients, being treated is the better option. This study demonstrates that our current approach of not over investigating women over 40 years of age and offering assisted reproduction where appropriate, still incurred the highest costs per additional live birth. We advise further research to investigate cost-effectiveness of treatment in this group before making firm recommendations for clinicians and policy makers. In women between the ages of 31 and 35 years in whom treatment associated cost per additional live birth were highest, there may be scope to improve the targeting of treatment strategies.

Unanswered questions and future research

Further research is needed to explore more efficient pathways of investigating and treating fertility problems in younger women. This can be facilitated by developing more accurate prediction models for spontaneous pregnancy which would allow a more targeted approach towards identifying who would benefit from early investigation and treatment. As the additional benefit of treatment versus no treatment in women over 40 was modest, it is worth exploring the cost effectiveness of treating women in this age group.

Conclusion

Over half of all women with fertility problems conceive within 5 years of referral to secondary care and over a quarter conceive spontaneously. Women with normal BMI and those who are younger tend to incur higher NHS costs as they are more likely to receive a greater array of investigations and treatment, despite having a greater chance of treatment independent pregnancies. The additional cost per additional live birth associated with treatment rises with decreasing BMI in women of all age groups, suggesting that it may be possible to identify a more targeted approach to the provision of treatment in women with normal BMI. Future research should focus on efforts to develop better prediction models for spontaneous pregnancy and the assessment of more tailored treatment pathways based on such models.

Acknowledgements

We thank the Aberdeen Fertility Centre Database Committee and the Aberdeen Maternal and Neonatal Databank Committee for giving us approval to use their databases. We thank the Data Management Team for extracting the required information from these databases. The views expressed in this paper represent the views of the authors and not necessarily the views of the funding bodies.

Author's Roles

SP, GS and SB conceived the project and designed it with input from JM and SW. DM designed the statistical analysis plan and analysed the data. SP and DM entered and cleaned the data and wrote the first draft. All authors contributed to the interpretation of the results and the final draft. GS designed the health economic methods and interpreted the results of the health economic analysis. Finally, both SP and DM contributed equally as authors in conducting the project and writing the paper.

Funding

This study was partly funded by an NHS endowment grant (Grant Number 12/48) and DM by a Chief Scientist Office Postdoctoral Fellowship (Ref PDF/12/06).

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi disclosure.pdf (available on request from the corresponding author) and there are no conflicting interests.

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