

GYNAECOLOGY

National survey of the current management of infertility in women aged 40 and over in the UK

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We conducted a national survey to identify the variation in the management of infertility in women aged 40 and over among the assisted conception units in the UK. A total of 44 out of 69 IVF units replied by filling in a questionnaire. Nearly half of the units (49%) offer treatment to this age group 6 months after trying for a pregnancy. As first-line management, 71.7% would offer conventional in vitro fertilisation (IVF) and 17.9% intra-uterine insemination (IUI). On average, the doctors would move on from IUI to the next step after three attempts. The survey revealed a mean age of 45 as the upper limit for application of IVF (own eggs), and 43% of the units will recommend three cycles of IVF using own eggs before moving to egg donation. Among interventions to improve outcome, 33.3% would consider blastocyst transfer, 5.9% pre-implantation genetic screening (PGS) and 3.9% assisted zona hatching (AZH).

Keywords: Infertility, assisted conception, older women

Introduction

The number of women seeking fertility treatment over the age of 40 increased 10 times from 1996 to 2006 in the UK. Women aged 40 accounted for 15.5% of all treatment cycles for the year 2006. However, the success rate of IVF in this age range has remained low. According to national UK data published by the human fertilisation and embryology authority (HFEA), the success rate (live-birth/cycles started) of IVF (own eggs) was 11.1% in the age group 40–42 (490 total live births); 4.6% in the age group 43–44 and 4% (nine total live births) in women over 44, during 2006. These data did not include natural cycles, PGD cycles and cycles where both fresh and frozen embryos were used in the same cycle (HFEA 2008). Data from the USA show similarly low success rates for women over the age of 40. The live-birth/cycles was 16.1% for age 40; 12.3% for age 41; 8.4% for age 42; 5.6% for age 43; 2.6% for age 44 and 0.8% for women aged over 44 for the year 2005 (CDC 2005).

Above the age of 39 years, the live-birth effectiveness after IVF treatment falls to 50% of the plateau level of younger women. Despite the fact that these women do not qualify for National Health Service-funded assisted reproduction treatment in the UK (with the exception of a very few primary care Trusts in the country, who fund treatment up until the age of 40), the number of women having fertility treatment in their 40s is steadily

increasing (National Collaborating Centre for Women's and Children's Health 2004).

We carried out a review of all available evidence, which showed that advances in assisted reproduction technology did not have a significant impact in improvement of the live-birth rate in women of advanced age (Marinakis and Nikolaou 2011).

Meta-analysis of randomised controlled trials (RCTs) has demonstrated that the application of assisted zona hatching (AZH) may improve the outcome in women with poor prognosis, including those with advanced reproductive age (Das et al. 2009). Data analysis shows that the implementation of day 5 embryo transfer improves the IVF success rates in all age groups, including women over 40. However, the included studies did not consider the cycles that a blastocyst failed to develop (Papanikolaou et al. 2008). Merely reaching the blastocyst stage of embryo development is a good prognostic factor. There is no evidence that adjuvant treatments could improve the fertility in women over 40. Recently, there has been increasing interest in the use of dehydroepiandrosterone (DHEA). However, the benefit of the DHEA supplementation was shown only in case series and reports (Casson et al. 2000; Barad et al. 2007).

More recent RCTs demonstrated that implementation of pre-implantation genetic screening (PGS) for selection of good quality oocytes in women of advanced reproductive age does not improve their likelihood of becoming pregnant (Staessen et al. 2004; Mastenbroek et al. 2007). Evidence shows that oocyte donation remains the only method that gives high success rates (around 50% live-birth rate per transfer), regardless of the recipient's age, until the age of 47 (HFEA 2008; CDC 2005; Toner et al. 2002; Stolwijk et al. 1997).

With this national survey, we aimed to identify the variation and the trends of the current management of infertility in women over the age of 40 among the assisted conception units in the country.

Methods

Setting

In the UK, the fertility clinics offering IUI, IVF and ICSI are inspected and licensed by the Human Fertilisation and Embryology Authority. The British National Healthcare Service does not fund assisted conception treatments over the age of 39 and only

an exceptionally few local healthcare authorities will fund treatment up to the age of 40. Therefore, fertility units that are managing NHS patients only were excluded from the study. NHS units that offer treatment to self-funding patients and private units were included in the survey. We identified 98 units licensed by the HFEA that offer treatments in women 40 years of age and over. From those, 69 units offer IUI, IVF and ICSI cycles and 29 units offer IUI only. We have excluded from the survey the 29 units that offer only IUI treatment to avoid bias both from the patients (which choose the specific Centre) and from the orientation of the Centres towards IUI or IVF.

Study population

We sent the survey questionnaire to all the 69 identified HFEA licensed fertility units offering IUI and IVF. We obtained the e-mail addresses of the clinical directors from the HFEA website and by contacting the units, when the information was not available on the website. To identify the profession and the exact level of the seniority of the person completing the questionnaire, we included a relevant question in the survey.

Survey development and statistical analysis

The questionnaire contained 17 questions with a choice of answers available for each question. In some questions, the participant could choose more than one answer and there was a free box for any relevant comments or to give an answer that was not available in the per-forma. The first 14 questions were about the management of infertility in women 40 years old and over. We included a question regarding the current status of NHS funding, asking if they would suggest a different age limit. We also included a question regarding the background of the healthcare professional participating in the survey and a question defining the geographical region of the unit. We approached all the units by e-mail during February 2009 and we re-sent the e-mail twice or more to the ones that had not answered. We posted the questionnaire to those units that had not replied by e-mail until end of March 2009. Finally, in April 2009, we did an additional telephone call to the units that had not replied. We analysed all the results by using a commercially available statistical package (SPSS 156 version 16.0.1).

Results

The overall reply rate was 63.7% (44 out of 69 IVF units). A total of 79.5% of the questionnaires were completed by 'Consultant Gynaecologists' who were specialists in reproductive medicine; 11.8% by 'Consultant Obstetricians and Gynaecologists'; 7.8% by doctors in training and 4.0% by 'Specialty' doctors.

Half of the units (51%) offer treatment to this age group 6 months after trying for a pregnancy and 29.4% after 12 months. The mean duration of sub-fertility before offering treatment is 7 months (CI: 1–12, SD \pm 4).

A total of 86.3% of the units replied that they include egg donation in their initial consultation, 62.7% the option of adoption and 58.8% the concept of creative life without children. At the first consultation, 94.1% of the units replied that they quote live-birth rates to women aged 40 and over, seeking fertility treatment. Regarding IUI and for the age group 40–42, 31.4% replied that they quote a success rate per attempt of 2–5%, and 19.6% of the units quote a success rate of 6–10%. For the age group of 43–44, nearly half (49%) quote a success rate of 2–5% and for the age group over the age of 44, 31.4% quote a success rate of < 1%; 17.6% quote a success rate of 2–5% and only 13.7% quote a success rate of 0%. The quoted success rates for IVF treatment per cycle were higher than those of IUI. For the age group 40–42, over

half of the units (54.9%) replied that they quote to their patients a success rate of 6–10% per cycle and 15.7% of the units quote a success rate of 11–15%. The majority of the professionals (60.8%) quote a success rate of IVF per cycle of 2–5% in the age group 43–44. A total of 35.3% of the units give a success rate of 2–5% per cycle and 33.3% of the units quote a success rate of less than 1% to women over the age of 44 who are planning to have a conventional IVF treatment.

We asked if units consider important, as part of the investigations, the ovarian reserve tests and specifically which ones. They all replied positively. More important appeared the FSH and the AMH as 88.2% and 70.6%, respectively, replied that they perform these tests as part of the initial investigations in women aged 40 and over. Half of the units (52.9%) implement the antral follicular count; 29.4% were in favour of testing the oestradiol levels and only 9.8% are testing the levels of inhibin-B (Table I).

With regard to first-line management, conventional IVF treatment appears the dominant choice of first-line management in the IVF units (71.7%) vs stimulated IUI (17.9%).

The survey showed a median age of application of IUI of 41 but there was significant variation among the replies. However, one-quarter of the units replied that they do not implement an age limit for application of IUI. This survey also revealed a median of 3 IUI cycles performed before moving to a different treatment. More specifically, 25.5% of the participants replied that they would not offer IUI treatment; 51% that they would offer 3 cycles; 7.8% would offer 2 cycles; 7.8% would offer 4 cycles and only 2% would offer up to 6 cycles (Figure 1).

With regard to IVF (own eggs), 17.6% of the specialists do not consider an age limit for its application. Only 3.9% would consider the age of 46 as an age limit when the majority (47.1%) would consider the age of 45 (median), and 13.7% the age of 44 (Figure 2).

We also identified after how many failed IVF cycles (own eggs) the medical staff would suggest the couple stop further attempts. A total of 15.7% of the specialists do not have a fixed upper limit in the number of IVF attempts. The majority (43.1%) of the units would recommend 3 cycles of IVF; 13.7% would recommend 2 cycles and 5.9% would consider 6 cycles, before moving to egg donation (Figure 3).

Among the techniques that might improve the live-birth rate, 33.3% of the specialists replied in favour of blastocyst transfer. Only 5.9% of the participants believe that the PGS can improve the birth rate in our study group and even less (3.9%) consider that the AZH can improve the outcome. Adjuvant treatments found a very small number of supporters. Only 5.9% of the units believe that aspirin and heparin might improve the live-birth rates and even less (3.9%) participants were in favour for DHEA supplement and steroids treatment (Table II).

Finally, we asked the specialists if they believe that the age limit of NHS funding for assisted conception treatments should change or not. A total of 68.6% replied that it should remain at the age of 39; 11.8% replied that it should increase up until the age of 40;

Table I. Are the ovarian reserve tests an important part of the initial investigations?

	Frequency	(%)
Yes	51	100.0
FSH	45	88.2
Oestradiol	15	29.4
Inhibin-B	5	9.8
Antral follicle count	27	52.9
AMH	36	70.6

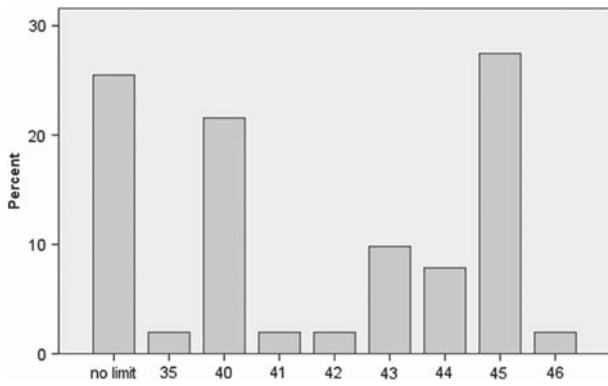


Figure 1. Age limit for application of IUI.

5.9% up until the age of 41; 7.8% up until the age of 42 and 5.9% up until the age of 43 (mean age 40; CI: 39–43).

Discussion

This national survey has revealed a variation as well as similarities in the management of infertility of women aged 40 and over among fertility centres in the UK.

All the participants have recognised a need of earlier intervention in this age group, even when the only issue is age (mean duration 7 months of unprotected sexual intercourse). However, on the basis of published data, if there is no other obvious reason for the delay in conception other than age, there is no evidence suggesting that the ART can improve the live-birth rate in women over 40 vs natural fertility.

Anthropological studies in populations with limited birth control showed that the biological capacity of a woman to conceive and carry a pregnancy at term declines with maternal age. This decline becomes steep from the age of 40 and is 0 at the age of 46 (O'Connor et al. 1998; Wood 1989). In addition, Leridon (2004) with a complex simulation model calculated the probability of conception under natural conditions within a year in relation to maternal age. According to this model at 30 years, 75% of women will conceive within a year and have a pregnancy ending in live-birth; when at 35 and 40 years, 66% and 44% will conceive within a year, respectively. These numbers appear far better than the IVF success rates in our study group.

On the other hand, ART has contributed to the better understanding of age-related decline of fertility, as it is clear from egg donation data that the main cause is the deteriorating oocyte quality rather than the sperm or the endometrium (Nikolaou 2008). HFEA data have shown that the success rates of IVF (own eggs) becomes

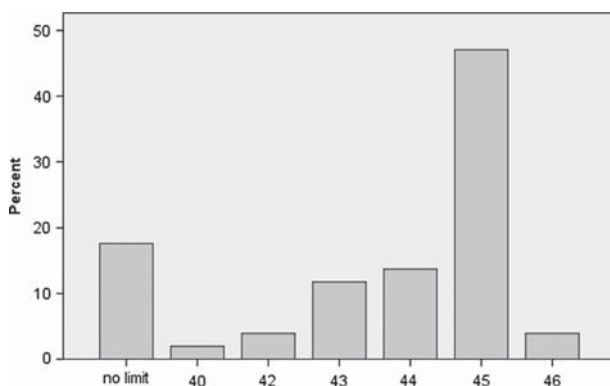


Figure 2. Age limit for application of IVF (own eggs).

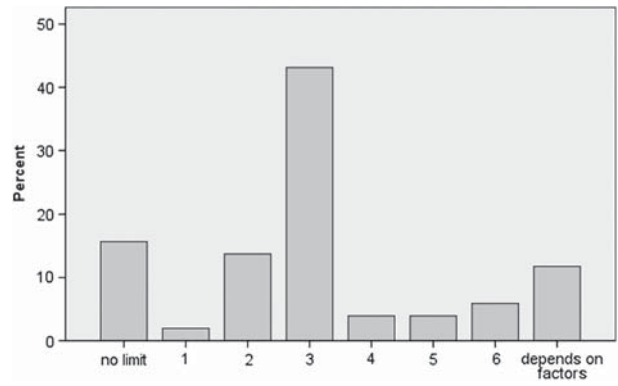


Figure 3. How many failed IVF attempts recommended before stopping IVF with own eggs.

extremely low over the age of 43. All the participants believe that the ovarian reserve tests are an important part of the initial investigations. However, studies have pointed out the failure of ovarian reserve tests to predict clinical pregnancy rates (Mol et al. 2006). Even the stimulation characteristics of the first IVF cycle, which is considered a good indicator of the ovarian reserve, has proved unhelpful in predicting the possibility of clinical pregnancy rate in women over 40. A study with 97 women aged 40–45, who underwent IVF showed that the women who conceived at the first cycle were the youngest of the group and those with the larger number of the oocytes recovered. The level of day 3 FSH, the duration of gonadotrophin stimulation, the serum E2 and progesterone levels on the day of hCG administration did not correlate with successful IVF (Homburg et al. 2009). Although these tests cannot predict the pregnancy outcome, they could help to individualise the protocol and therefore decrease the cancellation rate. The majority of the healthcare professionals replied in favour of IVF treatment vs IUI as first-line management (71.7% vs 17.9%).

Although the IVF success rates are published by the HFEA there is not a similar national report regarding the IUI treatment. There are only a few studies in the literature regarding IUI treatment with or without stimulation regarding women at 40 years of age and over. These studies showed that IUI has a lower success rate than conventional IVF. In a study of 281 women who underwent IUI treatment without ovarian stimulation, the cumulative probability of ongoing pregnancy following 3 cycles of IUI was 28.2% for women below 40 and 0.0% in women above 40. In a different study of women over the age of 40 who underwent IUI combined with ovarian stimulation, the pregnancy rate was 5% per cycle and the live-birth rate was only 1.4% per cycle. However, there is not a study to compare the success rates of IVF vs IUI in women 43 years old and over, where conventional IVF has a very poor outcome and possibly as poor as the IUI (Check et al. 2000; Frederick et al. 1994).

This survey has highlighted a variation in the limitation in the number of failed IVF cycles that the participant would offer before offering IVF with donated eggs. The majority of the

Table II. Interventions that might improve live-birth.

Interventions	Percentage of positive replies
Assisted zona hatching	3.9
Blastocyst transfer (day 5)	33.3
Preimplantation genetic screening	5.9
Mild or natural cycle IVF	0
<i>In vitro</i> maturation	2.0
Pre-treatment hysteroscopy and curettage	3.9

participants believe that interventions such as AZH, blastocyst transfer, in vivo maturation (IVM) and PGS do not improve the outcome. However, meta-analysis of RCTs has demonstrated that the application of AZH may improve the outcome in women with poor prognosis, including those with advanced reproductive age (Das et al. 2009). In addition, data analysis also supporting the implementation of day 5 embryo transfer as it has better success rates in all age groups including women over 40. But these results do not include the cycles that a day 5 blastocyst failed to develop (CDC 2005; Papanikolaou et al. 2008).

The guidance from the British Fertility Society regarding the application of PGS for advanced maternal age, which was based on two RCTs is discouraging. According to this guidance, clinicians should inform their patients that there is no evidence that PGS for advanced reproductive age improves their likelihood of becoming pregnant and in some cases, may result in a reduced chance of pregnancy (Anderson and Pickering 2008).

Adjuvant treatments found a very small number of supporters in this survey. There is nothing in the literature to suggest the opposite apart from small studies regarding the DHEA. A case-control study of 190 women with poor ovarian function and aged over 40 showed the cumulative clinical pregnancy rate was 28.1% in the treatment group vs 10.9% in the non-treatment ($p < 0.01$). Almost half of the pregnancies in the study group occurred spontaneously before the planned IVF treatment. Within the patients reaching IVF, the pregnancy rate in the treatment group was 20.6 vs 11.9% (Casson et al. 2000). The lack of larger studies and the difficulty to understand the biological mechanism of the DHEA could justify the doubts of its use from the majority of the UK units. Further research is required.

In the UK, women over the age of 39 seeking fertility treatment do not qualify for National Health Service-funded assisted reproduction treatment. The NICE Guideline Development Group based on complex cost-effectiveness modelling and on the HFEA statistics recommends that the upper age limit for NHS provision of IVF should be 39 years of age. Above the age of 39 years, the live-birth effectiveness after IVF treatment falls to 50% of the plateau level of younger women. Therefore, the age limit of 39 is the point where the cost per live-birth becomes double (National Collaborating Centre for Women's and Children's Health 2004).

In this survey, the majority of the participants (68.6%) replied that this age limit should remain at the age of 39. The funds to support an increase in the age limit could provide shorter waiting lists for the eligible ones, thus early fertility assessment and treatment when clinically indicated could increase the expectant success rate. However, governmental health programmes of egg donation as part of their services to women of advanced age seeking fertility treatment, could increase the success rates and possibly be more cost-effective when comparing it with conventional IVF.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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