What is the best treatment option for infertile women aged 40 and over?

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Abstract

Purpose To summarise the causes of decreased fecundity with age and review chronological vs biological ovarian ageing. To explore the clinician's means of assessing a woman's ovarian reserve. To review the recent literature on the effectiveness of different assisted reproductive technology (ART) techniques for women aged 40 and over and offer a single best treatment option.

Methods Pubmed and google scholar were searched for relevant articles using key words. Data were extracted based on authors, year, aims, sample and results.

Results Success rates for women aged 40 or over with clomiphene, IUI, IUI with FSH are all extremely low, at less than 1 % live birth per cycle. However, IVF offers a success rate of around 13.7 % per cycle.

Conclusion An exploration of the effectiveness of available treatment options for older infertile women using their own gametes suggests that IVF offers the best prospects of success. Attempting treatments other than IVF will delay conception unnecessarily.

Keywords Fertility · Infertility · Advanced maternal age · IVF · IUI · Diminished ovarian reserve · ART

Capsule The single best treatment option for infertile women = 40, using their own gametes, is IVF. Trying other fertility treatments will delay the chance of conceiving unnecessarily.

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Background

Delayed childbearing is becoming increasingly common in the western world. Demographic studies demonstrate that more women than ever before are leaving starting a family until they are 40 or older, in order to complete higher education, forge careers and establish financial security [1, 2]. Factors such as the development of the oral contraceptive pill in the 1960s and the legalisation of abortion have also had a role to play in this phenomenon, but interestingly it is now emerging that a societal awareness of the development of sophisticated treatments for infertility, is influencing women's decisions towards deferred childbirth. Whilst older mothers may benefit from a financial and social advantage, they are biologically disadvantaged by the natural decline in fertility with advancing age [3].

This trend is presenting new challenges to fertility specialists who are witnessing a corresponding rise in the mean age at which women first present with infertility [4, 5]. It is known that the outcome of assisted reproductive technology (ART) is adversely affected by advancing maternal age and the need to optimise treatment for these women has never been more pertinent [6]. Our objective was to outline the various causes of decreased fecundity with age, review the clinician's means of assessing ovarian reserve and explore the various fertility treatments available for women in this age group. Based on the limited published literature on this subject, we have proffered the best treatment option to optimize their chance of having a baby with their own eggs.

Causes of decreased fecundity with age

There is an evident gradual decline in female fecundity with age, particularly noticeable over the age of 30, accelerating between the ages of 35 and 40, reducing to almost zero by 45 [7, 8]. Classical studies of populations that don't use

contraception such as the Hutterites, show that childbearing declines steeply well before women enter their 40s [9]. This can be attributed to a reduction in successful conception rate and an increase in the miscarriage rate [10].

There is a decrease in ovarian reserve with age, caused by decreased numbers of oocytes and concomitant increase in the rate of oocyte aneuploidy resulting in reduced reproductive potential [11].

With regards to ovarian reserve, a woman is born with approximately 1–2 million oocytes in her ovaries, each enclosed in a layer of granulosa cells, in a primordial follicle, all arrested in the first meiotic prophase [12]. Of these, almost all of them (99.9 %) will undergo apoptosis, leaving a small fraction to resume meiosis at puberty to form the haploid gamete capable of fertilisation. As a woman ages, the absolute number of developing follicles declines at a rate that is bi-exponential to her age. The rate of follicle loss (atresia) more than doubles when her reserves fall below the critical level of 25,000 which occurs at approximately 37.5 years of age [13]. As the ovarian follicular pool decreases, women will increasingly experience infertility, cycle shortening, cycle irregularity and finally menopause [14]. Around 1 % of women will experience premature ovarian failure before 40 years of age. It follows that the women who undergo an earlier menopause, will also experience an earlier loss of fertility, leaving approximately 10 % of women who will have decreased ovarian function in their early to mid 30s [15].

In 1991, Navot et al. conducted a trial to determine the role of oocyte quality with advancing maternal age. They recruited women aged over 40 who had failed attempts at conception with their own oocytes and found that they had a significantly increased pregnancy and delivery rate with IVF from donated oocytes from younger women than with their own oocytes. Their data supports the idea that a decline in female fecundity with age is attributable largely to oocyte quality and is correctable by ovum donation [16].

Biological ageing vs chronological ageing

Of interest to those caring for older women seeking fertility treatment, is the assessment of her ‘biological ovarian age’. Studies have shown that ovarian ageing affecting oocyte quality and fecundity can occur independently of chronological age [17, 18]. Advancing age in women is associated with reduced oocyte quality, however biological age, which can be defined as a woman’s specific reproductive competence or ovarian reserve, can be entirely separate to her chronological age. It is hypothesized that the decline in oocyte quality as a woman ages is not simply due to the time-related effect of increased exposure to accidental damage, but rather that the defective oocytes were defective

from the very start, during fetal ovarian development [17]. These defective oocytes are less likely to be recruited for ovulation until relatively late in life, thus carrying an increased risk of aneuploidy and miscarriage [17].

Assessing ovarian reserve

Ovarian reserve can be defined as the population of non growing follicles (NGFs) within the ovary at any given age potentially capable of recruitment towards maturation. Assessing ovarian reserve in women seeking fertility treatment can be useful to determine her chance of a good ovarian response to stimulation and potentially, successful outcome with ART. This is particularly important with women aged 40 and over, as it provides information that may be useful in counseling the woman as to her chances of a successful outcome prior to starting treatment.

Currently there are no *in vivo* techniques available for counting NGFs and thus directly assessing a woman’s ovarian reserve, however a number of indirect methods exist. Ultrasound examinations to assess the antral follicle count and ovarian volume can be used. FSH has long been used as a marker of ovarian reserve and in 1989 Scott et al. performed the seminal study into the link between day 3 FSH levels and implantation rates. It demonstrated a dramatic decline in implantation rates between high and low day three FSH even when adjusted for age (mean age 35 years) [19]. Basal FSH levels are easy and cheap to obtain and the results require little skill to interpret which makes it an accessible test. However, only extremely elevated results are useful in predicting poor response to ovarian stimulation and non pregnancy [20].

More recently serum assays of anti mullerian hormone (AMH) has emerged as a more reliable and accurate way of assessing reserve. Recent studies into AMH have shown that increasing age and lower AMH levels both independently predict reduced oocyte yield following superovulation for assisted conception [21–23]. Thus AMH is emerging as an indirect approximation of age-related NGF populations and rates of recruitment. As such it provides moderate value in prediction of ovarian response in *in-vitro* fertilization (IVF), however may not be a good predictor of pregnancy [20]. Recently, Bhide et al. set out to establish whether there was a link between basal AMH and clinical pregnancy rates in women undergoing IVF/ICSI treatment and attempted to determine a cut off point, below which there are no pregnancies. The results showed an overall weak correlation between AMH and clinical pregnancy rates, however for women aged 40 and over, the correlation was significant. They concluded that AMH should not be used alone to refuse fertility treatment to women, but in conjunction with advanced maternal age is a strong independent predictor of clinical pregnancy rates [24].

Available ART options for older infertile women and their effectiveness

Often, the clinical evaluation of an infertile woman aged 40 or over, does not reveal specific findings. This puts these women into the unique subgroup of having ‘unexplained infertility’. It is likely that their reduced fertility potential is attributable to reduced oocyte number and quality as outlined earlier, but is also compounded by physical age-related factors such as endometriosis, which is more prevalent in older women, and fibroids [25].

Following the completion of investigations for infertility, a traditional stepwise approach to a woman’s treatment is undertaken. This involves several ovulation-induction regimes often combined with IUI for a period of 3–6 months, followed by IVF. In the following paragraphs, the benefits of these treatment options are examined for women aged 40 and over.

Ovulation induction with clomiphene citrate and intrauterine insemination

Clomiphene citrate has been used extensively for over 40 years in reproductive medicine and is a simple, inexpensive drug, which is used for the induction of ovulation in infertile women and also for the treatment of ovulating infertile women. The aim in women over 40 years is often to achieve 2 or 3 dominant follicles of at least 18 mm. Recent studies exploring the efficacy of clomiphene citrate as a treatment for infertile women have provided equivocal results. In 1998 Guzick et al. performed a retrospective review of the literature of women receiving clomiphene citrate +/- intrauterine insemination (IUI), and found the pregnancy rate was 6–8 % per cycle, compared to 2–4 % when not treated [26]. On the contrary, a recent large prospective study which randomised 600 women with unexplained infertility to clomiphene citrate, IUI or expectant management showed comparable results for all three arms in terms of delivery rates [27]. However, the mean age of participants in these studies was 31–32 years and results of clomiphene citrate involving delivery rates for women aged 40 and above are rarely reported and are seldom prospective studies.

In 2009, Tsafrir et al. reviewed the literature and examined the outcomes of ovulation induction with clomiphene citrate in women aged 40 and over in studies performed between 2002 and 2008 [25]. The results reveal a pregnancy rate of 1–4 % per cycle and the delivery rates are almost never reported. A further retrospective review of livebirths resulting from ovulation-induction and IUI in women aged 40 and over was performed by Corsan et al. in 1996. The results were similarly disappointing, reporting a low probability of livebirth in women undergoing this treatment aged

40–41 with no live births seen in women aged >42 years old [28]. Dovey et al. undertook a large retrospective cohort study examining the pregnancy rate per completed cycle of women receiving clomiphene citrate and IUI according to their age. In keeping with other studies, younger patients had higher pregnancy rates per cycle than older patients. In women aged 41–42, the pregnancy rate per cycle was 4.3 %, dropping to 1 % for women aged above 42 [29]. In summary, recent literature renders clomiphene citrate of little or no value to older women seeking infertility treatment, and swift referral for IVF should be sought after 1 or 2 failed cycles [30].

Ovulation induction with FSH and intrauterine insemination

Ovulation induction can also be achieved with FSH injections. The aim, as with clomiphene citrate, is to recruit 2 or 3 dominant follicles. Ovulation induction may encourage the recruitment of suboptimal follicles that may otherwise have not developed.

A retrospective study was carried out by Haebe et al. in 2002, which concluded that the live birth rate with IUI with ovulation induction for women aged 40–42 years old was 9.8 % (n=82) per insemination and thus demonstrated that IUI is an appropriate treatment for women in this age group. There were no live births in couples with a female age of >44. There was no significant difference in live births between ovarian stimulation protocols (GnRH-a and FSH, FSH, clomiphene, tamoxifen, clomiphene and FSH) [31]. Conversely, a retrospective study of 3 treatment centres by Tsafrir et al., demonstrated a pregnancy rate of 3 % per cycle with FSH and IUI and a delivery rate of 1 % per cycle [25]. A retrospective study undertaken by Merviel et al. to determine the predictive factors for pregnancy after IUI noted that the woman’s age was the strongest predictor of success in all indications, with an ongoing pregnancy rate per couple, per cycle, of 38.5 % for the under 30s and 12.5 % for the over 40s. However it should be noted that the actual numbers of women >40 in this study were small [32]. The discrepancy in pregnancy rates from these studies reflects the low birth rates in women of this age group, however all the published reports reviewed here highlight the overshadowing effect of age on ovulation induction and IUI results.

In-vitro fertilisation

The proportion of women aged 40 years and over entering IVF or intracytoplasmic sperm injection (ICSI) cycles comprises at least 25 % of all cycles undertaken in Europe [33].

The reason for this is that IVF, with or without ICSI appears to be the most efficient treatment for unexplained infertility [25]. IVF has the advantage of overcoming most male problems and female mechanical problems which are not uncommon in older women. Prospective randomised controlled trials comparing IVF to IUI and ovarian stimulation are rare, there only being two found in a 2005 Cochrane review [34]. However, there are numerous retrospective studies that have reported delivery rates of 20–30 % in IVF as compared with 10–15 % delivery rates in FSH plus IUI cycles in patients of all ages [35, 36]. In recent years, several large series have described IVF outcomes in older patients. On average, live birth rates were 8–10 % per started cycle in women over the age of 40 [25]. When these data are stratified by yearly age intervals, the results demonstrate a significant decline in live birth rate with each additional year in age [25]. Data recently published by the Human Fertilisation and Embryology Authority (HFEA) outlines the live birth rate, per IVF cycle started, using a woman's own fresh eggs, for the UK's licensed fertility clinics in 2009. In that year, a total of 13,364 babies were born as a result of IVF treatment in the UK. Between the ages of 38–39, the live birth rate is 19.2 % per cycle, dropping to 12.7 % for the age range 40–42, falling again to 5.1 % for ages 43–44, reducing to 1.5 % for women aged 45 and over [37]. A literature review in 2010 by Moragianni et al. examined the current literature on maternal age and cumulative live-birth rates (CLBR) with IVF. They reported 2 large studies of women older than 40 and 42 years using autologous oocytes with conservative CLBRs of 23 and 8.7 % respectively. They also reviewed a retrospective study of women aged 41–43, with favourable treatment prognoses who underwent a maximum of 3 IVF cycles with autologous oocytes. Conservative and optimistic CLBRs of 15.4 and 18.4 % respectively were reported [38]. Recently, Wiser et al. 2012, retrospectively reviewed the results of women aged >40 who underwent ovulation induction and IUI with

clomiphene citrate and gonadotrophin and compared them with those who underwent IVF. There were no clinical pregnancies in the clomiphene citrate group. Women in the gonadotrophin and IVF groups had clinical pregnancy rates of 2.6 % and 16.9 % and the live birth rates were 2.6 % and 13.7 % respectively [39]. Despite these relatively low live birth rates per cycle, IVF remains the most successful of all ART techniques for women aged 40 and over (Table 1). Attempting success with ovarian stimulation/ovulation induction will delay conception unnecessarily [39].

There appears to be little published literature available on ART outcomes in older infertile women in light of normal or abnormal ovarian reserves. Case report evidence suggests that IVF is the best option for women in this age group with reduced ovarian reserve.

Conclusion

The trend for delaying childbearing until later in life means that fertility specialists need to be well versed on the effectiveness of ART options for older women. The current literature supports that IVF is a woman's best chance of a successful ongoing pregnancy in this age group, and that opting for ovulation induction and IUI with either clomiphene or FSH can waste much precious time and thus reduce her chances of success with IVF.

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Table 1 Comparison of ART options for women aged ≥ 40

Treatments compared	Clinical pregnancy/cycle %	Live birth/cycle %	Study
Clomiphene	0–4 %	~0 %	Tsafrir et al. [25] Liu et al. [30]
IUI with clomiphene	1–4 %	<1 %	Tsafrir et al. [25]
	1–4.3 %	Unreported	Dovey et al. [29]
IUI with FSH	3 %	1 %	Tsafrir et al. [25]
IVF	16.9 %	13.7 %	Wiser et al. [39]

- hormone, age and number of ovulation induction/intra-uterine insemination cycles. *Hum Reprod.* 1996;11(6):1214–9.
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