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# Ageing and infertility: an overview

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## Abstract

In many modern societies, the proportion of women who delay childbearing beyond the age of 35 years has increased greatly in recent decades. They are falsely reassured by popular beliefs that advances in new reproductive technologies can compensate for the age-realted decline in fertility, but science cannot beat the biological clock. Age is the single most important determinant of male and female fertility, either natural or treated. The consequences of advancing maternal age are not only for the risk of natural and assisted conception, but also for the outcome of pregnancy. Female fertility has a 'best-before date' of 35, and for men, it is probably before age 45–50.

**Keywords:** *ageing, assisted reproduction, delayed childbearing, fertility, infertility*

## Introduction

The problem of infertility in Western societies has increased in several ways over the past 25 years. First, there are more infertile women in the population. Second, a larger proportion of infertile couples now seek treatment. Greater numbers seeking help, however, should not be interpreted as evidence that infertility rates are rising. Greater numbers seeking help are evidence that more help is available, more couples know that help is availabe and a big cohort is at the age where they are most likely to use that help [1]. Indeed, most women are currently delaying childbearing to an age where they are more likely to encounter problems having a child.

With expanding opportunities for higher education, careers and economic independence, combined with highly effective contraception, more and more young women are delaying childbearing until the fourth decade of life. Concurrently, a large cohort of women born during the 'Baby Boom' (1946–1964) have reached their late reproductive years, resulting in more women in this age group seeking assistance for infertility [2]. Thus, infertile women who are in their late 30s or early 40s now make up the majority of patients in many practices. Some women postpone motherhood because they think assisted reproductive technology (ART) is effective irrespective of the age of women and can compensate fully for the natural decline in fertility with age [3,4]. These facts together with decline of fertility with age have lead to an increased interest in the reproductive capacity of those aged women and a search for treatment options that may improve their fertility.

## Fertility demographic aspects

During most of the 20th century, the decline of fertility in Western societies went together with a trend to lower the mean age of maternity. Both trends mainly stemmed from the marked reduction in births of parity $\geq 3$. For example, in a country such as France, the mean age of women at maternity was 29.5 years in 1900 and 26.5 years in 1977. However, the trend in the mean age at birth began to change in the late 1970s, and the mean age at maternity was again 29.5 years by 2000 [5]. Similarly, in Canada, the average age that women deliver a first child has risen from 24.6 years in 1970 to 29.1 years in 1999 [3].

The impressive recent rise in the mean age at maternity is the result of postponing the first (and subsequent) births rather than a rise in fertility (the number of births per woman) at later ages. In France, an upward trend did appear at the end of the 1970s in the rates for the 35–39 and 40–49 years age groups, but these rates in 2000 were still far below those observed in 1900 [5]. Similar changes can be observed in most developed countries and thus, in Canada, most women will deliver their first child above the age of 30 with the proportions of first births after age 34 increasing from 6% (1975) to 18% (1995) to 25% in 2005 [3]. Also in the United States, the past 10–15 years have seen a remarkable shift in the demographics of childbearing. The number of first births per 1000 women 35–39 years of age increased by 36% between 1991 and 2001, and the rate among women 40–44 years of age leaped by a remarkable 70% [6].

On the other hand, another major change has simultaneously occurred in that births are now more strictly planned, whatever their rank. A birth to a woman aged 35 years is often her first or second birth, or the first birth in a new union. A few decades ago a birth at 35 years of age was usually a birth to a woman of higher parity, and it was not always wanted [5]. Therefore, it is likely that many couples who are also trying to have a child at around this age do not succeed because of the decline in fecundity with age as discussed later.

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In fact, it is well established that female fertility begins to decline many years prior to the onset of menopause despite continued regular ovulatory cycles. Although there is no strict definition of advanced reproductive age in women, it is generally accepted as the age of $\geq 35$ years [2,6].

## Mechanisms of reproductive ageing

As previously reviewed [2,4,5,7], it seems clear that despite some decline in male fertility with age, particularly $>50$ years, there is no absolute age at which men cannot father a child. Semen volume, sperm motility and sperm morphology decrease with age, whereas the data concerning sperm concentrations are conflicting [7]. Fertility is thus more related to the age of the female than the male partner.

This notwithstanding, a recent study [8] investigating the effect of maternal and paternal age on pregnancy and miscarriage rates after intrauterine insemination and analysing more than 17,000 treatment cycles, concluded that the quantity and motility of spermatozoa in the final preparation used for insemination had a positive effect on the outcome, as classically observed in the past. It was found that advanced maternal age had a negative effect on the pregnancy rate and was associated with increased miscarriage rate. More interestingly, an exactly parallel effect was found for paternal age ($>40$–$45$ years). The impact of increased age on necrospermia and sperm DNA structure is postulated as a probable direct cause of this paternal effect.

Another recent study [9] investigated whether male age influences embryo development and reproductive potential in ART cycles. One thousand twenty-three male partners participating in anonymous oocyte donation cycles were included in this study. A significant increase in pregnancy loss, decrease in live birth rate and decrease in blastocyst formation rate were noted in men $>50$ years of age. There was no significant difference in implantation rate, pregnancy rate or early embryo development through the cleavage stage (demonstrated by fertilisation rate, embryo cleavage rate, percentage of non-fertilised or polyspermic embryos, rate of embryo arrest or seven or more cell embryo development on day 3). Men $\leq 45$ years of age had significantly more semen volume and more motile sperm than men $>45$ years of age. There was no significant change in sperm morphology or concentration. After controlling for female age with use of the donor oocyte model, it was concluded that male age $>50$ years significantly affected pregnancy outcomes and blastocyst formation rates [9].

The decrease in fertility with female ageing is mainly due to a decreasing number of oocytes after birth. Female infants have 6–7 million oocytes at 20 weeks of gestation, 1–2 million oocytes at the time of birth, about 250,000 oocytes at menarche, 25,000 oocytes at 37 years of age and only a few hundreds or thousands at the end of their reproductive life [4]. It has been proposed a biphasic model of oocyte disappearance from birth to menopause. The total oocyte number declines bi-exponentially with age and the loss of follicles accelerates around the age of 37–38 years. The progressive loss of oocytes from foetal life through menopause is a normal process. Genetic influences remain the primary determinants of natural menopause, although environmental factors may play some roles in gonadal senescence. In this respect, it is to note that very recently, five genome-wide association studies of the timing of menarche and menopause have now taken us beyond the range of candidate gene and linkage studies [10]. The list of new genetic associations identified for these two traits should shed light on the mechanisms of ovarian aging, as well as breast cancer and other diseases associated with reproductive lifespan. These genetic associations may not offer direct clinical applications today, but they are a step towards understanding premature menopause, reduced fertility and other direct features of the reproductive lifespan.

The age-associated decline in female fecundity and increased risk of spontaneous abortion are largely attributable to abnormalities in the oocyte [2,11]. The meiotic spindle in the oocytes of older women frequently exhibits abnormalities in chromosome alignment and microtubular matrix composition. Higher rates of single chromatid abnormalities in oocytes, as well as aneuploidy in pre-implantation embryos and ongoing pregnancies, are observed in older women. The higher rate of aneuploidy is a major cause of increased spontaneous abortion and decreased live birth rates in women of advanced reproductive age. The poor quality of oocytes in aged women is clearly illustrated by the improved pregnancy rates obtained with donated oocytes [11].

Age-related uterine factors may also play a role in the decline in fertility with increasing age. This is suggested by a retrospective cohort study evaluating the role of recipient age on the outcome of $>3000$ donor egg cycles [12]. Although no significant linear relationship between oocyte recipients' age and pregnancy rate, implantation rate or miscarriage rate was observed, pregnancy and implantation rates were reduced and miscarriage rate increased from 45 year of age onward. A retrospective cohort study of aggregated national cycles of donor egg therapy that are collected by Society for Assisted Reproductive Technology and the Centres for Disease Control and Prevention and analysing recipients of embryos (17,339 cycles) derived from donated eggs between 1996 and 1998, showed that success of donor egg therapy was remarkably constant among recipients aged 25 years through those in their late forties. At higher ages, declining rates of implantation, clinical pregnancy and delivery were seen, along with small increases of pregnancy loss. From this study, it was concluded that the success of donor egg therapy is unaffected by recipient age up to the later 40s, after which they begin to decline. Although recipient age *per se* is likely to be the major cause of this effect, other factors may contribute to this observation [13].

The role of diminished uterine receptivity and its potential mechanisms with increasing woman's age is, however, a matter of controversy. Thus, some authors claim that the reduced endometrial receptivity may be related to reduced uterine blood flow with increased age, a decreased sensitivity to progesterone effects or the presence of uterine fibroids, which again become more common with age [4]. On the contrary, others emphasise that the prevalence of uterine pathology, such as fibroids and endometrial polyps, increases with age, yet there is little evidence that uterine factors have a significant impact on age-related infertility. It is also stressed that age does not appear to have a significant effect on morphological or histological responses of the uterus to steroid stimulation [2].

## Effect of ageing on the reproductive outcome

The consequences of advancing maternal age are not only for the risk of natural and assisted conception, but also for the outcome of pregnancy even in normal women (i.e. those getting pregnant spontaneously).

It has been reported that *risk of foetal death*, and in particular *spontaneous abortion*, increases with increasing

maternal age [14,15]. It is well known from early studies that previous spontaneous abortions and multigravidity are also well-established risk factors for spontaneous abortion in subsequent pregnancies [16]. However, these factors are highly correlated and the association between age and spontaneous abortion reflects both biological mechanisms and forces of selection, the significance of the association is expected to change over time [17]. As discussed earlier, decades ago, older pregnant women were mainly those with low fecundity or high parity but, at present, many women delay childbearing for social reasons. To evaluate what the effect of maternal age is on foetal death (spontaneous abortion, ectopic pregnancy, stillbirth) when taking into account a woman's reproductive history, a prospective register population-based linkage study involving 1,221,546 pregnancy outcomes in 634,272 was carried out in Denmark [17]. All women with a reproductive outcome (live birth, stillbirth, spontaneous abortion leading to admission to hospital, induced abortion, ectopic pregnancy or hydatidiform mole) from 1978 to 1992 were included. Main outcome measures were age related risk of foetal loss, ectopic pregnancy and stillbirth, as well as age-related risk of spontaneous abortion stratified according to parity and previous spontaneous abortions. This was done using data from the population based Danish health registries, which cover the population of Denmark. This allowed the authors to control for the confounding effects of reproductive history and calendar period. Overall, 13.5% of the pregnancies intended to be carried to term ended with foetal loss. At age 42 years, more than half of such pregnancies resulted in foetal loss. The risk of a spontaneous abortion was 8.9% in women aged 20–24 years and 74.7% in those aged 45 years or more. High maternal age was a significant risk factor for spontaneous abortion irrespective of the number of previous miscarriages, parity or calendar period. The risk of an ectopic pregnancy and stillbirth also increased with increasing maternal age [17].

The risk of Down's syndrome and other *chromosomal abnormalities* is increased with increasing maternal age as a result of deterioration of egg quality with advancing maternal age [4]. Numerous karyotyping studies and molecular cytogenetic studies have been reported to date, providing a large body of data on the incidence and the distribution of chromosomal abnormalities in human female gametes, but also displaying a great variability in results, which may be essentially attributable to the technical limitations of these in situ methods when applied to human oocytes [18]. Essentially, the most relevant analyses have led to the estimate that 15–20% of human oocytes display chromosome abnormalities, and they have emphasised the implication of both whole chromosome non-disjunction and chromatid separation in the occurrence of aneuploidy in human oocytes. The effect of advanced maternal age on the incidence of aneuploidies has also been investigated in human oocytes. Most previous studies have failed to confirm any relationship between maternal age and aneuploidy frequency in human oocytes, whereas the more recent reports based on large samples of oocytes or polar bodies have provided evidence for a direct correlation between increased aneuploidy frequency and advanced maternal age, and have clarified the contribution of the various types of malsegregation in the maternal age-dependent aneuploidies [18].

Both adolescents and women of advanced reproductive age comprise distinct groups of obstetrics patients. Each has special needs and is susceptible to different *obstetric risks and complications*. Pregnant women over the age of 34 have an increased risk for a poor obstetric outcome. To examine pregnancy outcomes in women age 40 or older, a large population study involving 1,160,000 women delivered during a 2-year period was carried out using data from the California Health Information for Policy Project, which consists of linked records from the birth certificate and the hospital discharge record of both mother and newborn of all births that occurred in acute care civilian hospitals in California [19]. The study population consisted of all women who delivered at age 40 or over (24,032 or 2% of the women). The control population was women who delivered between age 20 and 29 years during the 2-year period. Gestational age at delivery, birth weight, mode and type of delivery, discharge summary and birth certificate demographics, birth outcome, pregnancy and delivery data were considered. Virtually every complication of gestation was increased in older patients compared with young controls. Thus, nulliparous women aged ≥40 years had a higher risk of operative delivery than nulliparous women aged 20–29 years (61% vs. 35%). Rates of birth asphyxia, foetal growth restriction, malpresentation and gestational diabetes were significantly higher among older nulliparas (6, 2.5, 11 and 7%, respectively) compared with rates among control nulliparas (4, 1.4, 6 and 1.7%, respectively), and there were similar significant increases among older multiparas (3.4, 1.4, 6.9 and 7.8%, respectively), compared with younger multiparous controls (2.4, 1, 3.7 and 1.6%, respectively). Mean birth weight of infants delivered by older nulliparous women was significantly lower than that among nulliparous controls, whereas mean birth weight in the group of older multiparas was no different than that among younger multiparous controls. Gestational age at delivery was significantly lower among older nulliparas compared with nulliparous controls, and similarly lower among older multiparous women, compared with multiparous controls. Therefore, according to this and other studies [20] it seems clear that increasing maternal age is independently associated with specific adverse pregnancy outcomes and increasing age is a continuum rather than a threshold effect.

Fertility is the rate of childbearing in a population. *Fertility rates* in populations that do not practice contraception give the best estimation of the ability of normal women to conceive. In a seminal paper based on 10 different populations living between the 17th and the 20th centuries that did not use contraceptives, Menken et al. [21] investigated the effect of maternal age on the average rate of pregnancy. These authors nicely showed that fertility remains relatively stable through 30 years of age, at more than 400 pregnancies per 1000 exposed women per year, and then begins to decrease substantially. By 45 years of age, the fertility rate is only 100 pregnancies per 1000 exposed women.

The most important determinant of a couple's fertility is the woman's age. Thus, *infertility rate* increases with age and age affects the *success rates of infertility treatments* [22,23]. Age of females partners markedly influenced the results of the so-called traditional treatment of infertility (i.e. those available before the era of assisted reproduction), and pregnancy rates were significantly lower in women over 35 years old as compared to younger patients [22]. Similarly, there is also a marked age-related decline in success rates when using modern ART for treatment of infertility; this is discussed later.

## Effect of ageing on assisted reproduction outcome

As discussed earlier, fecundity has been reported to decline in women over 30–35 years of age. Two major problems

encountered in studying variations in fecundity as a function of a woman's age are as follows: (1) the need to separate the effect of the woman's age from associated variables such as coital pattern and husband's age, and (2) the woman's age itself, which could result in bias, since time introduces a type of selection. *Artificial insemination with donor semen* (AID) offers an opportunity to control certain variables in the study of female fecundity over time thus providing the best means of minimising the effects of associated variables and sources of bias.

In a landmark study, 2193 nulliparous women who were receiving AID from 1973 to 80 at the Centres d'Etude et de Conservation du Sperme Humain (CE-COS) and whose husbands were totally sterile (thus avoiding important bias with respect to male fecundity and coital frequency) were studied [24]. The women were divided into four age groups: 25 years old or younger ($n = 371$), 26–30 ($n = 1079$), 31–35 ($n = 599$) and 35 or older ($n = 144$). At the end of the study period, the women were categorised into four groups, depending on the outcome: success (all pregnancies occurring during the study period), lost to follow-up (if the result of the last AID cycle was unknown), open case (result of last AID cycle was known but the next insemination procedure had not yet taken place) and dropout (discontinued treatment). The cumulative success rates were calculated after 12 cycles with the life table technique adapted to AID as if there were no dropouts (theoretical cumulative rates). The Mantel-Haenzel test was used to compare the curves obtained from the cumulative rate as a function of the number of treatment cycles for the various age groups. The four curves differed significantly (chi-square = 15.72, with 3 degrees of freedom; $p < 0.01$). The curves for the two age groups under 30 were very similar. Overall, the study shows that a decrease in fecundability (conception rate per cycle) as a function of a woman's age is slight but significant after 30 years of age and marked after 35 years. The probability of success of AID for 12 cycles declined to 61% (from 74% for those under 31 years old) for the 31–35 age group ($p < 0.03$) and to 54% (from 74% for those under 31 years old) for those over 35 ($p < 0.001$).

Recent data generated from European registers by the European Society of Human Reproduction and Embriology (ESHRE) [25] show that in women $< 40$ years of age, 18,515 treatments AID resulted in 3498 pregnancies giving a pregnancy rate per insemination of 18.9%. In women at 40 years or above, the corresponding figures were 2053, 189 and 9.2%.

*Intrauterine insemination using husband/partner's sperm* (IUI) mainly in association with ovulation induction (OI) is, at present, a frequently used first choice of the assisted conception techniques that may be useful for the treatment of infertile women with patent fallopian tubes [26]. The most common indications for IUI are some of the less severe forms of male factor infertility and unexplained infertility. The latter is a frequent condition found in couples where women are in the advanced reproductive age group [27]. Unfortunately, however, IUI plus OI has limited efficacy for women over 40 with otherwise unexplained infertility, yielding a per cycle delivery rate of 5% or less (range: 1.4–5.2%). This compares with a live birth rate per cycle of 17–22% for women under 35 and 8–10% for women aged 35–40 [2].

Similarly, data from ESHRE registers indicate that in women $< 40$ years of age, 120,613 treatments with IUI and OI resulted in 15,154 pregnancies, giving a pregnancy rate of 12.6% per procedure. In women at $> 40$ years, the corresponding figures were 8,295,617 and 7.4% [25].

The presence of male factor, tubal disease, endometriosis or pelvic adhesions would argue for proceeding directly to *in-vitro fertilisation and embryo transfer* (IVF-ET) in women of advanced reproductive age. Pregnancy rates from IVF are generally higher than from IUI/OI but also decline significantly with age. In fact, a woman's age is the most important factor affecting the chances of a live birth when her own eggs are used. Success rates decline with each year of age and are particularly low for women 40 or older.

According to the Asssited Reproductive Technology Success Rates-Centers for Disease Control and Prevention [28], live birth rates per IVF cycle were 39.6%, 37.8%, 31.8% and 16.1% in women aged 25, 30, 35 and 40 years, respectively. This percentage dropped steadily with each 1-year increase in age. For women older than 44, the percentages of live births was a little less than 1%. In a review of 431 initiated IVF cycles in women $\geq 41$ years, there were no clinical pregnancies in women $\geq 45$ years and no deliveries in women $\geq 44$ years of age [29]. This age-related decline in IVF success is related to decreased ovarian responsiveness to gonadotropins and, more importantly, to a marked decline in embryo implantation rates.

ART imply the pharmacological induction of multiple follicular recruitment to obtain multiple oocytes and embryos. The most widely used protocol for ovarian stimulation in IVF cycles has involved the administration of gonadotropins under pituitary suppression with GnRH agonists (the so-called long down-regulation protocol) which not only increases pregnancy and live-birth rates, but also allows flexible timing for oocyte recovery and greatly simplifies IVF treatment [30,31]. However, a number of women are found to respond poorly or not at all to this standard treatment, such patients are referred to as 'low or poor responders'. Low response to ovarian stimulation frequently reflects an age-related decline in reproductive performance (older patients with an abnormal endocrinological profile) and its incidence increases in parallel with woman's age. Thus, data from the Assisted Reproductive Registry in the United States [32] indicate that in couples with no male factor infertility undergoing IVF treatment, cancelled cycles because of poor response to ovarian stimulation were 10.3, 14.9, 20.1 and 25.3% among women aged $< 35$ years, 35- to 37-years, 38–40 years and $> 40$ years, respectively. Irrespective of the protocol used, the treatment of poor responders results in a low pregnancy rate, unless the couple makes the difficult decision to use donor eggs [33].

On the basis that embryonic aneuploidy is likely the major reason for implantation failure in older women, it has been proposed the use of preimplantation genetic screening (PGS) to improve implantation rates and IVF outcome. In PGS, embryos are analysed for aneuploidies and only embryos that are euploid for the chromosomes tested are transferred. However, as recently stressed by the American Society for Reproductive Medicine [34] available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with advanced maternal age. Similarly, the American College of Obstetricians and Gynecologists [35] has emphasised that current data does not support a recommendation for PGS for aneuploidy using fluorescence in situ hybridisation solely because of maternal age. In fact, the systematic review of the literature and metanalysis indicates that PGS for aneuploidy in women with poor prognosis or in general *in vitro* fertilisation programme, not only does not increase but may be even associated with lower rates of ongoing pregnancies and live births [35,36].

An addtional important issue is the *increased risk for adverse pregnancy outcomes after ART* for those fortunate to become pregnant. The National Institute of Child Health and Human Development held a workshop to summarise these risks [37]. It was concluded that although it is not possible to separate ART-related risks from those secondary to the underlying reproductive pathology, the overall increased frequency of *obstetric complications*, including preterm birth and small for gestational age neonates, as well as *maternal complications*, such as preeclampsia, gestational diabetes, placenta previa, placental abruption and caesarean delivery should be discussed with the couple.

Overall, considering all the above discussed matters, it becomes evident that advances in *new reproductive technologies cannot compensate for the aged-related decline in fertility*. In fact, it is estimated that ART compensates for only half of the births lost by postponing a first attempt of pregnancy from 30 to 35 years of age, and <30% after postponing from 35 to 40 years of age [38]. Therefore, ART in its present form cannot make up for all births lost by the natural decline of fertility after age 35 years and thus, women aged 35–40 years should turn to ART sooner [1]. Remarkably, women are largely aware of the risks and complications of delaying childbirth, but erroneously believe that ART can reverse the effects of age [39]. There is a need to provide accurate information in the community. Recently, the American Society for Reproductive Medicine [40] has stressed that there is not yet sufficient data to recommend ovarian tissue of oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women.

## Concluding remarks

In many modern societies, the proportion of women who delay childbearing beyond the age of 35 years has increased greatly in recent decades. They are falsely reassured by popular beliefs that advances in new reproductive technologies can compensate for the age-realted decline in fertility. Yet age is the single most important determinant of male and female fertility, either natural or treated. Therefore, it must seriously considered that 'age is an incurable disease' (Seneca) [41] and science cannot beat the biological clock. The consequences of advancing maternal age are not only for the risk of natural and assisted conception, but also for the outcome of pregnancy. Female fertility has a 'best-before date' of 35, and for men, it is probably before age 45–50. Therefore, prevention of infertility campaigns such as that launched by the American Society of Reproductive Medicine [42] and including the reproductive aging as a main theme are warranted.

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