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Delayed Childbearing: Effects on Fertility and the Outcome of Pregnancy

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Abstract

In modern societies, the proportion of women who delay childbearing beyond the age of 35 years has greatly increased in recent decades. They are falsely reassured by popular beliefs that advances in new reproductive technologies can compensate for the age-related decline in fertility. Yet age remains the single most important determinant of male and female fertility, either natural or treated. The consequences of advancing maternal age are not only relevant for the risk of natural and assisted conception, but also for the outcome of pregnancy. Although the absolute rate of poor pregnancy outcomes may be low from an individual standpoint, the impact of delaying childbearing from a public health perspective cannot be overestimated and should be in the agenda of public health policies for the years to come. This review summarizes available evidence regarding the impact of delaying childbearing on fertility and pregnancy outcomes.

Introduction

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 number 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 [1]. 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 [2, 3]. These facts together with decline of fertility with age have led to an increased interest in the reproductive capacity of those aged women and a search for treatment options that may improve their fertility.

The consequences of advancing maternal age, however, 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). Remarkably, many women are unaware of the potential consequences of delayed childbearing. The association between increasing maternal age and perinatal complica-

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tions affects the healthcare sector in a substantial way. Thus, there is a need for information about the consequences of delayed childbearing and a need to adjust maternal and obstetric care. More information about obstetric consequences of delayed childbearing is needed both for obstetricians and fertile women.

This review highlights the effects of delayed childbearing on fertility and obstetric and perinatal outcome.

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 ≥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 [4]. 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 [2].

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 [4]. 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 [2]. 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 1,000 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% [5].

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, 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 [4]. 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 below.

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 ≥35 years [1, 5].

Mechanisms of Reproductive Ageing

As previously reviewed [1, 3–6], 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 [6]. Fertility is thus more related to the age of the female than the male partner.

This notwithstanding, a recent study investigating the effect of maternal and paternal age on pregnancy and miscarriage rates after intrauterine insemination and analyzing 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 [7]. 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 investigated whether male age influences embryo development and reproductive potential in ART cycles [8]. 1,023 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 fertilization rate, embryo cleavage rate, percentage of non-fertilized or polyspermic embryos, rate of embryo arrest, or seven or more cell embryo development on day 3). Men ≤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 signifi-

cantly affected pregnancy outcomes and blastocyst formation rates [8].

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 hundred or thousand at the end of their reproductive life [3]. 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 fetal 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 [9]. The list of new genetic associations identified for these two traits should shed light on the mechanisms of ovarian ageing, as well as breast cancer and other diseases associated with reproductive life span. 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 life span.

The age-associated decline in female fecundity and increased risk of spontaneous abortion are largely attributable to abnormalities in the oocyte [1, 4]. 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 preimplantation 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 [4].

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 >3,000 donor egg cycles [10]. 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 years 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 Centers for Disease Control and Prevention and analyzing 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 40s. 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 [11].

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 [3]. On the contrary, others emphasize 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 [1].

Effect of Ageing on Fertility and Infertility Treatment

Fertility Rate

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 ten different populations living between the 17th and the 20th centuries that did not use contraceptives, Menken et al. [12] 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 1,000 exposed women per year, and then begins to decrease substantially. By 45 years of age, the fertility rate is only 100 pregnancies per 1,000 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 as reported next.

Success Rates of Infertility Therapy

Age markedly affects the success of infertility treatments [13, 14]. 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 [13]. Similarly, there is also a marked age-related decline in success rates when using modern ART for treatment of infertility; this is discussed below.

Effect of Ageing on Pregnancy Rate and Outcome in Assisted Reproduction

Artificial Insemination with Donor Semen (AID)

As discussed above, 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: (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. AID offers an opportunity to control certain variables in the study of female fecundity over time thus providing the best means of minimizing the effects of associated variables and sources of bias.

In a landmark study, 2,193 nulliparous women who were receiving AID from 1973 to 1980 at the Centres d'Etude et de Conservation du Sperme Humain (CECOS) and whose husbands were totally sterile (thus avoiding important bias with respect to male fecundity and coital frequency) were studied [15]. The women were divided into four age groups: 25 years old or younger (n = 371), 26–30 (n = 1,079), 31–35 (n = 599), and 35 or older (n = 144). At the end of the study period, the women were categorized 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 ($\chi^2 = 15.72$, 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 ($p < 0.001$). It is noteworthy that the variable under study, the age of the woman, can itself result in bias, since time introduces a type of selection. In AID this possibility is especially high if a husband has reduced fecundity but is not sterile; if his wife is very fecund, she may be precluded from study because she has previously conceived. This bias becomes more pronounced with the age of the women studied. Thus, a feature of this study [15] is that only women with azoospermic husbands were included, thus avoiding this possible bias.

Recent data generated from European registers by the European Society of Human Reproduction and Embryology (ESHRE) [16] show that in women <40 years of age, 18,515 AID treatments resulted in 3,498 pregnancies giving a pregnancy rate per insemination of 18.9%. In women at 40 years or above, the corresponding figures were 2,053, 189 and 9.2%.

Intrauterine Insemination Using Husband/Partner's Sperm (IUI)

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 [17]. 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 [18]. 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 [1]. 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% [16].

In vitro Fertilization and Embryo Transfer (IVF-ET)

The presence of male factor, tubal disease, endometriosis, or pelvic adhesions would argue for proceeding directly to 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 Assisted Reproductive Technology Success Rates [19], 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 ≥41 years, there were no clinical pregnancies in women ≥45 years and no deliveries in women ≥44 years of [20]. 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 implies the pharmacological induction of multiple follicular recruitment in order 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 [21, 22]. 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 [23] 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, 35–37, 38–40 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 [24].

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 analyzed 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 [25] and the ESHRE PGD Consortium steering committee [26], 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 (2009) [27] has emphasized that current data does not support a recommendation for PGS for aneuploidy using fluorescence in situ hybridization solely because of maternal age. In fact, the systematic review of the literature and meta-analysis indicates that PGS for aneuploidy in women with poor prognosis or in general in vitro fertilization program not only does not increase but may be even associated with lower rates of ongoing pregnancies and live births [27, 28].

Pregnancy Outcomes after Assisted Reproductive Technology

An additional 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 summarize these risks [29]. 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 (SGA) neonates, as well as *maternal complications*, such as preeclampsia, gestational diabetes, placenta previa, placental abruption, and cesarean 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 [30]. 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 [31]. Remarkably, women are largely aware of the risks and complications of delaying childbirth but erroneously believe that ART can reverse the effects of age [32]. There is a need to provide accurate information in the community. Recently, the American Society for Reproductive Medicine [33] has stressed that there is as yet insufficient data to recommend ovarian tissue of oocyte cryopreservation for the sole purpose of circumventing reproductive ageing in healthy women.

Impact of Maternal Age on Obstetric and Perinatal Outcomes

Advanced maternal age has been associated with increased obstetric morbidity and interventions. In addition, perinatal complications are reported to be higher in this patient population. The impact may be modest from the standpoint of the individual patients, but have important public health implications. This section will summarize current evidence on perinatal outcomes associated with advanced maternal age.

First-Trimester Complications

Abortion

It is long known that the risk of abortion increases substantially with age. The risk for admission due to abortion in patients aged 35–44 increases by 40% with respect to younger women according to national registries [34]. 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 [35]. High maternal age was a significant risk factor for spontaneous abortion irrespective of the number of previous miscarriages, parity, or calendar period. Thus, although maternal age was highly correlated with parity and reproductive history, this study demonstrated that the effect of maternal age on the risk of spontaneous abortion was independent. Advanced age has also been reported to be associated with an increased risk of miscarriage in patients presenting with pain, bleeding, or both in the first trimester of pregnancy. In a total of 2,026 women, multivariate analysis demonstrated that only extremes in age (<25 and >35) and heavy bleeding were significant risk factors to eventually present miscarriage [36].

The independent effect of age is very difficult to ascertain. Abnormal chromosome number is the most common and well-documented cause of miscarriage, and therefore the increase in the rate of abortion is influenced by definition by the known increase in the rate of aneuploidies [37]. Non-chromosomal factors include endocrine and anatomic abnormalities, thrombophilia and immunologic factors [38], and ageing is likely to influence in the prevalence of most. Thus it seems plausible that there is a multifactorial association between age and spontaneous abortion.

Ectopic Pregnancy

In a large Danish population-based study [35], the risk of EP increased from 1.4% at 21 years to 6.9% in patients of 44 or later. The effect could partially be explained by a higher prevalence of subfertile patients with an increased risk to have an ectopic pregnancy. However, other studies have corrected for this potential effect and have shown that the majority of the increase is attributable to age alone [39]. From a national registry in France, the rate of hospital admissions due to EP per hundred pregnancies increased from about 1.5% in patients aged 20–34 to some 2.5% in 35- to 44-year-olds [40]. In the same study, the rate of patients requiring surgical treatment increased significantly after 35 years of age.

Fetal and Obstetric Complications and Postnatal Outcome

Fetal Malformations, Genetic and Chromosomal Defects

The association of delayed childbearing with an increased rate of chromosomal defects is probably the best known effect of age on fetal disorders, and for this reason we will not dedicate much space to discuss this issue. It must be remembered that the age dependency is confined to aneuploidies, that is, numerical anomalies, whereas structural abnormalities do not show age-related differences [41]. As aneuploidies are by far the most frequent chromosomal anomalies, the impact of this association has conditioned public health policies over the last two decades. Age is the strongest predictor of numerical chromosomal anomalies, and particularly of Down syndrome, in very different settings [37, 42] and consequently it has been incorporated in any combination of predictive factors used nowadays. The weight of age remains whatever combination of markers is tested [43]. On the negative side, the psychological association between age and Down syndrome is so strong that it remains a common reason to indicate an amniocentesis in settings where clear criteria for screening policies have not been defined [44, 45].

Conversely, no association between most single-gene anomalies and age has been reported, although the rarity of these conditions prevents to perform studies in large sample sizes. In addition, there is good evidence that there is no association between maternal age and most non-chromosomal malformations, which is further confirmed by recent European-wide studies [46].

Preterm Delivery

The association between maternal age and prematurity is one of the best demonstrated ones. The risk of prematurity in a large population-based study in France in 1995 increased from 4.5% in women aged 30–34 to 5.6% at 35–39 and 6.8% in patients aged over 40 [47]. This risk was unchanged with respect to data from the early 1980s in the same population. The data are in line with studies performed in Canada [48], Sweden [49] and the United States [50, 51]. In the study conducted in Canada, on 160,000 deliveries of singleton newborns, the risk of prematurity increased from about 5% in women aged 25–34 years to 6.2% among those 35–39 years old and 7.2% in patients over 40 [48]. It is important to stress that in most of these studies the analyses were adjusted for the coexistence of other obstetrical complications and preexisting maternal diseases, which by definition are found in higher frequencies in older women. Therefore, there is conclusive evidence that advanced maternal age is independently associated with increased rates of preterm delivery. If we add the indirect effects of the increased prevalence of complications which in turn are associated with increased preterm birth, such as chronic hypertension, diabetes, and other maternal conditions, the impact of delayed childbearing on prematurity cannot be overestimated.

Intrauterine Growth Restriction

It is difficult to differentiate the rate of prematurity from that of intrauterine growth restriction (IUGR) alone. Many studies report the rates of 'low birth weight' [50, 52] as defined by absolute birth weight, which does not reflect the true incidence of IUGR. Thus, we will describe studies reporting the proportion of SGA newborns, defined as the proportion of fetuses born smaller than the 10th centile for gestational age. While this definition still includes a proportion of constitutionally small normal fetuses, thus without placental insufficiency, it provides a reasonable approach to the incidence of IUGR [53].

When studies defining SGA according to centiles adjusted for gestational age are analyzed, most, but not all, report independent effects of age on the incidence of IUGR. In a large population study discussed above, Joseph et al. [48] described that the rates of SGA increased progressively with maternal age. In addition, the relation between maternal age and IUGR was demonstrated in a population-based study including only singleton pregnancies with documented absence of fetal malformations [54]. IUGR was defined as a birth weight <10th percentile for gestational age and gestational age was confirmed by early ultrasound. The study compared 824 cases with IUGR with 1,648 controls randomly selected from the same population. After multivariate analysis which included among others black race, chronic hypertension or pregestational diabetes, maternal age >35 and >40 years were independently and significantly associated with IUGR with OR of 1.4 and 3.2, respectively. The contribution of age has also been indirectly supported by studies evaluating the impact of other diseases on IUGR. For instance, Iqbal et al. [55] reported that maternal age was an independent cofactor for the presence of IUGR among women with HIV disease. In contrast to these studies, another large population study in Canada, which evaluated more than 40,000 birth registries, found no relationship between maternal age and SGA [56]. The authors suggested that the increase in low birth weight observed in their study was secondary to the changes in preterm delivery. Finally, and to add a bit of further confusion, fetal growth in the first trimester, which is a predictor of IUGR and poor neonatal outcome, is paradoxically *positively* correlated with maternal age [57, 58], hence older mothers have longer first-trimester crown-to-rump length.

In conclusion, available evidence generally supports the notion that advanced maternal age is independently associated with increased IUGR even after correction of some known confounding factors. This association does not reflect a primary effect on smaller embryos, but the effect is rather manifested during the third trimester. This might suggest an increased rate of placental insufficiency, but this notion has not been investigated.

Multiple Pregnancy

The increased incidence of multiple pregnancy possibly accounts for a substantial deal of the negative impact of delaying childbearing on perinatal outcomes. In spite of their relatively low frequency, multiple pregnancies amount to a significant proportion of adverse perinatal outcomes [59, 60]. The proportion of multiplets in older pregnant women increases further due to the combined effect of the use of assisted reproduction techniques, but

there is a clear age-specific effect. Already in 1970, before the wide use of assisted reproduction, in France the rate of multiple pregnancies increased from 5.4 per 1,000 in patients aged <20 years while it was 14.3 per 1,000 in women between 35 and 39 [61]. Studies conducted recently confirm the independent association between increased age and the rate of spontaneous multiple pregnancy [62, 63].

Intrauterine Fetal Death

Perinatal mortality is certainly increased in women delaying childbirth if only the association of concomitant risk factors such as preterm birth and IUGR was taken into account. But again, in addition to the influence of associated factors, there is evidence to support an independent effect of age. The available evidence was recently summarized in a systematic review which selected 31 retrospective cohort and 6 case-control studies according to pre-established quality criteria. In most of the studies included, the analysis was adjusted for important confounders such as parity, hypertension or diabetes. There was not uniform definition of advanced age, but in general 'older women' were defined as those above 35 years of age. Advanced maternal age was significantly associated with an increased risk of stillbirth in 77% of the cohort and all 6 case-control studies, with relative risks ranging 1.20 to 4.53 in older with respect to younger women [64].

Cerebral Palsy and Neurocognitive Disorders of Prenatal Origin

The impact of delayed childbearing on neurodevelopmental problems has not been considered in previous reviews. The increase in prematurity and IUGR should have an impact on the prevalence of neurodevelopmental sequelae, considering the strong association of these two complications with the prevalence of both serious adverse neurological events and milder, but much more prevalent, neurocognitive disorders [65]. In support of this hypothesis, in a study conducted in Sweden, a cohort of 65 children born to mothers with a mean age of 39.4 years was compared with 55 age-matched children born to mothers with a mean age of 27.9 years. Fine-motor problems, visuoperceptual dysfunction and attention deficit signs were significantly more common among children of older mothers [65]. These abnormalities are also characteristic of prematurity and IUGR [66], and therefore it seems plausible that a higher prevalence of these complications could largely explain the results. Aside from the indirect association given by the increase in high-risk conditions, one population-based study conducted on a cohort of 334,339 infants born at 36 weeks' gestational age or beyond described that maternal age >35 years was independently associated with an increased incidence of cerebral palsy [67].

In relation with psychiatric disorders, there is strong evidence from a considerable number of population studies that advanced maternal (and in this case also paternal) age is associated with a higher risk of autism [68, 69]. In addition, in an interesting study performed in 1982 in Sweden by the same group as above, psychotic children and adolescents tended to have mothers (and fathers) older than the average in the general population [70], which led the author to suggest that these patients could have some kind of 'organic' background factors. Unfortunately, we have not been able to find similar studies conducted more recently.

Maternal Morbidity and Mortality

Diabetes and Chronic Hypertension

There is an expected association of advanced maternal age with gestational diabetes and pregnancy-associated hypertension [71, 72]. In most pregnancies these entities have little or no effect on pregnancy outcome per se, but they increase the risk of other complications. In addition, both are associated with well-known long-term cardiovascular effects, although such association is likely mediated by common predisposing factors rather than by a causal relationship.

Peripartum Obstetric Complications and Maternal Morbidity

The rate of cesarean section increases substantially with age [73, 74]. The rates of cesarean section increase steadily from teenage years upwards, and contrary to other complications described above, there does not seem to be a limit from which the risk increases steeply. The increase is likely the combination of physiological changes with increasing maternal age [75], which may raise the perceived potential for complications among patients and health providers [76]. Concerning postpartum hemorrhage and particularly the risk of postpartum hysterectomy, there is an association with maternal age, which is mostly due to the association with the strongest predictors of risk, i.e. multiparity, abnormal placentation and previous cesarean section [77]. When the risk is confined to uterine atony, some studies identified age as the risk factor for hysterectomy [78].

The risk of medical complications is also significantly increased, although the magnitude of such increase is not impressive. For instance, in a large study conducted in the United States, the risk of venous thromboembolism was 38% higher for women aged 35 and older [79]. Likewise, the incidence of other serious complications during pregnancy, even if extremely low, increases severalfold in pregnant women beyond 35 and 40 years of age [80, 81].

Maternal Mortality

An increase in the risk of dying is one of the many disadvantages of becoming older, and therefore it is not surprising that there is a strong trend for increasing maternal mortality in women of older age in all developed countries [82]. Different studies agree in reporting stable rates until 35 years with a steep increase from then onwards, with relative ratios ranging from 2 to 7 for women above 35 years and from 6 to 30 in patients aged 40 or more [40, 83]. The higher maternal mortality rates are obviously explained by a higher frequency of serious obstetric complications, which results from a combination of a primary increase in their incidence together with the inevitable higher prevalence and severity of chronic conditions occurring with ageing.

Conclusion

In modern societies, the proportion of women who delay childbearing beyond the age of 35 years has greatly increased in recent decades. They are falsely reassured by popular beliefs that advances in new reproductive technologies can compensate for the age-related decline in fertility. Yet age remains the single most important determinant of male and female fertility, either natural or treated. Therefore, it must be seriously considered that 'age is an incurable disease' (L.A. Seneca) [84] and science cannot beat the biological clock. The consequences of advancing maternal age are not only relevant for the risk of natural and assisted conception but also for the outcome of pregnancy. Although the absolute rate of poor pregnancy outcomes may be low from an individual standpoint, the impact of delaying childbearing from a public health perspective cannot be overestimated and should be in the agenda of public health policies for the years to come. 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 [85] and including the reproductive ageing as a main theme are warranted.

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