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REVIEW ARTICLE

Reproductive ageing—turning back the clock?

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Abstract

Background Unintended childlessness is a distressing, and often unintended, consequence of delayed childbearing and reproductive ageing. The average maternal age at first birth has risen steadily in many industrialised countries since the 1980s. There are many societal factors involved in the decision to postpone motherhood. As a result, many women are postponing having children until it is too late. In this review, we aim to summarise the reasons behind delayed childbearing, the impact of delayed childbearing and the scientific advances that seek to reverse reproductive ageing and ensure reproductive autonomy for women.
Methods An extensive literature search of PubMed was conducted to include all published articles on delayed childbearing and the consequences of reproductive ageing. Secondary articles were identified from key paper reference listings.
Conclusion If the current reproductive trends continue, many women will find themselves in the harrowing position of being unintentionally childless. In addition, many will inevitably turn to assisted reproductive technologies in an effort to protect and preserve their reproductive autonomy. However, it is not always possible to reverse the effects of reproductive ageing.

Keywords Assisted reproductive technology · Fertility · Oocyte vitrification · Ovarian reserve · Reproduction

Trends in reproductive timing

Over the past four decades, the number of women postponing pregnancy has continued to increase, significantly impacting the age of first-time mothers. Mean maternal age at first birth rose by 1.5 years between 1980 and 1993 in EU countries [1], and a continued shift toward delayed childbearing is supported in other population studies [2–5]. Ireland is no exception to this trend. According to the HSE Perinatal Statistics report in 2013, the average age of women giving birth rose from 30.8 years in 2004 to 32.1 years in 2013. Births to primiparous women aged 40 years and older accounted for 1.8% of births in 2004 compared to 3.5% in 2013 [6].

The transition into parenthood is a major life event, and many prospective parents deliberate its timing carefully [7]. Maternal age at first birth often influences the total number of births that a woman will have in her life and has far-reaching implications for society including size, composition and future growth of the population [8]. This phenomenon of delayed childbearing continues to expand, despite well-documented evidence of a decrease in fertility and fecundity with increasing age [9].

Determinants of delayed childbearing

The trend of delayed childbearing and the consequential increase in unintended childlessness are multifaceted in origin. Level of education, parenthood "readiness", prolonged adolescence and absence of a suitable partner have all been shown to be contributory factors [7, 10–14].

This trend is dominant among women with at least a high school education in the USA [3]. Findings from the National Childhood Development Study in the UK indicate that more intelligent women are more likely to remain childless by the end of their reproductive years. One-standard-deviation increase in childhood general intelligence decreases a women's odds of parenthood by 21–25% [15]. From the Swedish population register, predictors of being childless were related to growing up in a large city, having well-educated parents, no siblings and not having moved from home at age 22. Principal

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reasons for not having children were not yet being prepared for parenthood, followed by not having met a suitable partner [2]. Relationship status and feeling "ready" were also dominant themes in qualitative work by Cooke that assessed determinants of delayed childbearing [10], supported in a meta-synthesis by the same group [16].

The impact of the media on reproductive choices and trends cannot be overstated. A study of women aged 15–49 years performed by Westoff and colleagues evaluated the number of children born in the preceding 5 years, and identified a consistent decrease that correlated with television exposure. The authors concluded that television exposes viewers to features of modern life that often are in competition with traditional attitudes toward marriage and the family and have the potential to influence reproductive behaviour [17]. Media, as a whole, is recognised to profoundly influence the definition of what is "normal" and "reasonable" behaviour in health-related issues [18]. Based on a qualitative, exploratory analysis of media representations of maternal age and older mothers in the UK, Mills proposes that media portrayals of older mothers are likely to have a positive impact on public perceptions of delayed childbearing. Three main themes emerged from their study: (1) delaying childbearing was often a conscious choice and allowed women to achieve other goals, (2) age was not a barrier to childbearing and (3) with advances in medical technology, reproductive problems could be addressed [4]. The positive sentiments of the media portrayal of older mothers could be interpreted as an endorsement of delayed childbearing and could well be contributing to the current trend.

Another powerful determinant of delayed childbearing is the belief that assisted reproductive technology (ART) can reverse the biological clock. The growing popularity and use of ART has given women the false impression that it is possible to manipulate the biological clock regardless of age [19]. Many women incorrectly believe that ART will be successful up until menopause [19–22].

Impact of delayed childbearing

Fertility

It is well-documented that fecundity and fertility decrease with advancing age. Epidemiological studies have demonstrated that fertility starts to decline at 30 years of age and is largely diminished by 40 years [23, 24]. Probability of pregnancy is twice as high for women aged 19–26 years compared to women aged 35–39 years [9]. Delayed childbearing until after 35 years of age has doubled the incidence of involuntary childlessness in the last two decades [25]. From a simulation model of reproduction, Leridon et al. report that 14% of women will remain childless if they delay starting to try to conceive until the age of 35 and 34.8% if they delay to age 40 [26].

Reasons for age-related fertility decline include reduced oocyte numbers and quality, reduced embryo quality and an increase in miscarriage rates due to aneuploidy. In a study by Rosen and colleagues, antral follicle counts as a marker of ovarian reserve were significantly lower in infertile women than in control women across age groups up to 40 years of age [27]. Reduction in oocyte quantity is also accompanied by a reduction in oocyte quality. Approximately 10–30% of fertilised human oocytes are thought to be aneuploid, with the majority being either trisomic or monosomic. Aneuploidy is the most commonly identified chromosome abnormality in humans, occurring in at least 5% of all clinically recognised pregnancies [28]. Approximately one-third of all miscarriages are aneuploid, making it the leading known cause of pregnancy loss. Of conceptions that survive to term, aneuploidy is the primary genetic cause of intellectual disability [28]. Age is the strongest predictor of numerical chromosomal anomalies [29]. Approximately 2% of clinically recognised pregnancies of women under the age of 25 is affected by trisomy, compared to 35% for women over the age of 40 [28]. Franasiak et al. reviewed 15,169 consecutive trophectoderm biopsies screened for chromosomal abnormalities and showed that aneuploidy increased in a predictable fashion after 26 years of age [30].

The origin of aneuploidy has inspired much interest and research over the past two decades. Most trisomies occur as a result of errors of the first meiotic division of the oocyte, which is only completed at the time of ovulation [28]. The link between increasing maternal age and risk of aneuploidy has been well-documented historically, and the association between increasing maternal age and Down syndrome was recognised as early as 1933 [31]. The ageing process also correlates with an increase in mitochondrial dysfunction, impacting on oocyte quality; however, further research is needed in this area [32]. Similarly, the impact of increasing maternal age on diminished uterine receptivity has not yet been fully elucidated [33].

Delayed childbearing is one of the main contributory factors to the increasing use of ART in many countries [34]. Despite advances in the field, modern technology remains unable to completely reverse the biological clock. Success of IVF and embryo transfer declines with each year and is particularly low in women over 40 years of age [35–37]. Therefore, the application of ART as a solution to age-related fertility decline will not compensate for all births lost as a result of this phenomenon [38].

Foetal outcomes

The impact of delayed childbearing and reproductive ageing on foetal outcomes is significant at every gestational age and outcome studied. Anderson et al. demonstrated that 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 [39]. This study also demonstrated that the effect of maternal age on spontaneous abortion risk was independent of parity and reproductive history. Advancing maternal age is further linked to an increased risk of ectopic pregnancy [40, 41] and to increased rates of preterm delivery, even when studies were adjusted for the coexistence of other obstetrical complications and preexisting maternal diseases already associated with older age groups [42–45].

When adjusting for confounding factors, intrauterine growth restriction (IUGR) is seen in higher proportions in older mothers than younger mothers [44, 46]. Furthermore, there is an increased risk of intrauterine foetal death with advancing maternal age [47]. A population-based study of 334,339 infants demonstrated that maternal age greater than 35 years was associated with an increased incidence of cerebral palsy [48].

As older prospective mothers turn to ART to avoid unintended childlessness, cumulative negative foetal impacts are anticipated. ART (IVF/ICSI) is associated with a higher incidence of prematurity, IUGR, foetal malformations and genomic-imprinting diseases [49–53].

Maternal outcomes

The significant risks to the health and life of the mother that result from delayed childbearing have also been well-documented [54]. While older women are expected to have naturally developed more chronic illnesses by the time of pregnancy, this still does not account for all the negative, adverse events that are linked to increasing maternal age [55]. The increased risk of maternal mortality is most notable after 35 years of age [56]. Maternal mortality most often occurs as a result of cardiovascular disease, diabetes, placental abruption and complications arising from operative deliveries [57]. There is also a significant maternal morbidity burden associated with advancing maternal age, with women aged 35 years or older displaying increased risk of gestational diabetes and pregnancy-associated hypertensive diseases [58, 59].

Scientific advances with the aim of circumventing unintended childlessness while protecting genetic autonomy due to delayed childbearing

In view of this unprecedented increase in delayed childbearing and its consequential unintended effects, several important advances now offer women an opportunity to avoid this potentially devastating position. Ovarian reserve testing and the advent of oocyte vitrification (egg freezing) for social reasons may now allow women to postpone childbearing without risking the situation of unintended childlessness or having to resort to the route of oocyte donation in an attempt to become a parent. Adjuncts to ART may also give some hope to prospective parents in the future. These include the further development and improvement of preimplantation genetic screening (PGS) and the possible identification of novel non-invasive biomarkers of egg quality. Interestingly, our recent study showed that Irish women are very open to the use of modern technologies in an attempt to avoid unintended childlessness [60].

Oocyte donation

Oocyte donation has become a well-established practice in reproductive medicine and has been used to treat women with premature ovarian failure and those women presenting with advanced reproductive age [61]. This form of ART has continued to result in excellent success rates [62]. This is essentially as a result of the decrease in reduced oocyte quality owing to a very young, healthy donor population [61]. Despite excellent success rates, the technique is viewed by some as ethically contentious [63]. There is concern relating to the recruitment of healthy young women for donor programmes, often enticed by financial reward [61]. Furthermore, there is a lack of longitudinal studies documenting the long-term effects of treatment on donors, recipients, children born or the families created [61].

Ovarian reserve testing

Ovarian reserve refers to the size of the ovarian follicular pool and is determined by the net result of the original size of the primordial follicle pool, the natural rate of atretic loss and the influence of any insult or injury to the ovary that may accelerate follicle depletion [64]. It is documented that up to 10% of women in their mid-30s are involuntarily sterile due to diminished ovarian reserve [65]. Ovarian reserve testing refers to efforts to measure the reproductive potential of an individual as a function of the quantity of remaining oocytes [66]. A recent study in the Merrion Fertility Clinic sought to evaluate risk factors for women with low anti-Müllerian hormone (AMH) levels indicating low ovarian reserve and demonstrated that the presence of clinical risk factors will only identify half of women at risk of low ovarian reserve [67].

AMH levels are currently the best available measure of ovarian reserve [66]. Granulosa cells of the preantral and small antral follicles are responsible for producing AMH [68]. Serum AMH levels have shown great sensitivity to ovarian ageing and significant correlation with antral follicle count [69]. Ovarian reserve can have a significant effect on future reproductive potential and on success rates with assisted reproduction [70, 71]. However, other studies contradict the efficacy of AMH testing in predicting immediate natural conception [72]. Serum AMH has been employed as a useful predictor of ovarian response to controlled ovarian stimulation (COS) [73], and as a marker of oocyte and embryo quality during COS [74, 75].

At present, serum AMH testing is not recommended as a population-based screening test for young women, although this prospect is increasingly discussed in medical circles [64]. The ethical and clinical impacts of AMH testing and ovarian reserve screening are complex and multifaceted and have not been fully elucidated. Individualised ovarian reserve screen may have the potential to impact a woman's reproductive behaviour, rather than generic, non-personalised age-related fertility advice. Some studies have shown that, if empowered with their individual ovarian reserve status, the decisions women make regarding further education and career may be different [76, 77]. Knowledge of a low ovarian reserve status may help women choose to prioritise motherhood earlier than planned, or to consider oocyte vitrification. While there are potential psychological benefits to be gained by ovarian reserve testing when a result reflects adequate ovarian reserve, the unexpected diagnosis of a critical ovarian reserve level could be devastating. A recent qualitative study in the Merrion Fertility Clinic explored the psychological impact of AMH testing and demonstrated the significant negative impact of communicating a low AMH result to women undergoing fertility investigations.

Oocyte Vitrification

Oocyte vitrification or "social egg freezing" to combat one's own reproductive ageing is a relatively new practice. However, it has been used for over a decade as an efficient, effective technique in oocyte donation programmes [78–80]. A large retrospective cohort study of children born after use of vitrified or fresh oocytes concluded that the process of vitrification had no clinically relevant adverse effects on obstetric and perinatal outcomes after adjusting for potential confounders [81]. As a result of increasing evidence for the safety of the procedure, it has recently been reclassified as non-experimental by the American Society of Reproductive Medicine (ASRM) and the European Society for Human Reproduction and Embryology (ESHRE) [82, 83], and is increasingly being offered to women in an attempt to avoid unintended childlessness without affecting genetic autonomy.

Vitrification or cryopreservation refers to the cooling of cells and tissues to sub-zero temperatures to stop all biologic activity, so that they can be preserved for future use. Initial success was limited by cellular damage, ice crystal formation or excessive dehydration. The use of cryoprotectants subsequently improved cryopreservation techniques, and the first human birth from a frozen oocyte was reported in 1986 [84]. The original slow freeze technique has now been largely replaced by vitrification, which uses high concentrations of cryoprotectants and rapid cooling to avoid ice crystal formation. The human metaphase II oocyte is an extraordinary but very fragile cell, owing to its large water content, larger size and chromosomal rearrangement. Susceptibility to spindle apparatus damage by ice formation may be dependent on patient age [85], as 80% of oocytes are aneuploid at age 40 years [86].

A retrospective multicentre study of 1468 women undergoing oocyte vitrification for fertility preservation demonstrated that at least 8–10 metaphase II oocytes were necessary to achieve a reasonable chance of pregnancy. The authors concluded that optimal oocyte number should be individualised when the woman is aged 36 years or older. Rates of oocyte survival, clinical pregnancy, ongoing pregnancy and livebirth were all significantly higher in the under 35-year age group, i.e. the age at time of oocyte vitrification [87]. However, the demographic profile of women presenting for fertility preservation using oocyte vitrification shows that they are doing so at a suboptimal age and consulting too late for treatment [87]. It is important, when counselling the cohort of women that attend for fertility preservation, to use data applicable to them and to avoid false reassurances by quoting survival and pregnancy rates from donor oocytes from very young women [88, 89].

Adjuncts to ART

With an ever-increasing need for ART, the focus on success rates has never been more to the fore. To improve ART outcomes for women who delay childbearing, PGS and biomarkers of oocyte and embryo quality may be of benefit.

Preimplantation genetic screening

PGS refers to the selection of euploid embryos for transfer in an effort to increase the chances of a healthy pregnancy. This technique was proposed as far back as the early 1990s [90]. The main indications for this technique include advanced maternal age, repeated implantation failure, recurrent miscarriage and severe male factor infertility, as these specific patient groups have a higher chance of producing aneuploid embryos.

There is extensive international debate regarding the value and place of PGS. A meta-analysis by Chen et al. concluded that PGS cycles, when compared to those using only morphological methods of embryo assessment, improved rates of implantation, clinical pregnancy, ongoing pregnancy and live birth while reducing miscarriage rates [91]. However, these findings have not been reproduced in prospective randomised controlled trials [92–94]. Ongoing developments and technical improvements in PGS (which include progression from fluorescence in situ hybridization (FISH) to current use of massive parallel sequencing) [90] may affect these conclusions.

While PGS has been proposed for women of advanced maternal age, there are a number of studies demonstrating that older women do not benefit, and that PGS may actually reduce pregnancy rates in this cohort [92]. This may be explained by false-positive aneuploid detection in trophectoderm biopsies,

due to mosaicism in blastocyst-stage embryos. Although such embryos are typically discarded, studies have shown that mosaic embryos are in fact still capable of producing healthy babies [95]. The widespread, clinical application of PGS for this aged patient cohort in particular has become a very contentious issue in IVF. Without substantial evidence proving the effectiveness and safety of the procedure, the routine use of PGS should not be advocated.

Potential biomarkers of oocyte quality and early embryonic development

The discovery of an accurate, non-invasive and cost-effective predictive test of the development potential of an oocyte or embryo is an important goal of much ongoing research worldwide. However, this concept of predetermining an oocytes' potential remains a major obstacle [96]. The potential implications of such a discovery could have major impacts not only on IVF treatment, but also on oocyte vitrification for the purposes of fertility preservation. We know that only a small number of the oocytes retrieved in an IVF cycle have the potential to develop into a viable embryo resulting in a live birth [97]. As a result, in some cases, multiple embryos are transferred per treatment cycle with a view to increasing pregnancy rates. Increasing pregnancy rates then occur at the expense of increased risk of complications for both mother and offspring [98]. A predictive test of developmental potential to aid in oocyte selection could therefore have a major impact on the practice of embryo transfer, embryo storage and oocyte vitrification. In contrast to the current policy of vitrifying a minimum of 8–10 metaphase II oocytes to ensure a reasonable chance of achieving pregnancy [87], it may be possible to provide a more individualised approach in counselling women about the need for further stimulation cycles to achieve the optimal number of oocytes for them.

Conclusion

If current societal reproductive trends continue, many women will find themselves in the harrowing position of being unintentionally childless. Many will inevitably turn to ART in an effort to protect and preserve their reproductive autonomy. Technological advances, such as ovarian reserve testing, oocyte vitrification, PGS and the advent of biomarkers of oocyte and embryo quality, offer increasing hope to this group. However, it is clear that, even with this technology, the adverse effects of reproductive ageing on the female biological clock are not reversible. Compared to natural conception at an early age (< 30 years), technology is, at best, a second-rate option. It is therefore incumbent upon health agencies and healthcare professionals to provide the public with appropriate education and information and to be more proactive in enabling young women to access these services if required. On a broader level, society must also address some of the issues that prevent young people from pursing parenthood at a time when they have a reasonable chance of fulfilling their intentions of having a family.

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest statement The authors declare that they have no conflict of interests.

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