Elective oocyte cryopreservation for age-related fertility decline

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Abstract

Purpose Women who pursue fertility at an advanced age are increasingly common. Family planning and sexual education have traditionally focused on contraception and prevention of sexually transmitted diseases. A focus should now also be placed on fertility awareness and fertility preservation. This manuscript aims to give an update on the existing evidence around elective oocyte cryopreservation, also highlighting the need for fertility education and evidence-based, individualized counselling.

Methods A thorough electronic search was performed from the start of databases to March 2020 aiming to summarize the existing evidence around elective egg freezing, the logic behind its use, patient counselling and education, success rates and risks involved, regulation, cost-effectiveness, current status and future perspectives.

Results Clinician-led counselling regarding reproductive aging and fertility preservation is often overlooked. Elective oocyte cryopreservation is not a guarantee of live birth, and the answer regarding cost-effectiveness needs to be individualized. The existing studies on obstetric and perinatal outcomes following the use of egg freezing are, until now, reassuring. Constant monitoring of short-term and long-term outcomes, uniform regulation and evidence-based, individualized counselling is of paramount importance.

Conclusions Elective oocyte cryopreservation is one of the most controversial aspects of the world of assisted reproduction, and a lot of questions remain unanswered. However, women today do have this option which was not available in the past. Elective oocyte cryopreservation for age-related fertility decline should be incorporated in women’s reproductive options to ensure informed decisions and reproductive autonomy.

Keywords ART · Cryopreservation · Egg freezing · Fertility preservation · Slow freezing · Vitrification

Introduction

Family planning has changed as the role of the woman has evolved during the last few decades. Globally the average age when women have their first child has significantly increased [1, 2]. Higher education, career aspirations, financial reasons and changes in society and in human relationships have all contributed to this change [3, 4]. Delaying childbearing has, however, a significant detrimental impact on female reproductive potential leading to age-related fertility decline and subsequent infertility and is not always by choice. Involuntary childlessness confers significant psychological burden [5] which has even been compared to the emotional distress of cancer diagnosis [6].

The decline in female reproductive potential is inevitable and irreversible. Age confers a bi-exponential decline in the quantity of oocytes especially after the age of 37 [7]. Egg quality and chromosomal integrity of the resulting embryos are also affected after the age of 35. Advanced maternal age is the most important risk factor for early miscarriage [8] with age-related risk of miscarriage being 51% at 40–44 years of age and 93% after the age of 45 [9]. Success rates after one cycle of in vitro fertilization (IVF) are reported around 30% for women below 35, but this percentage significantly declines after this age leaving almost no chance of live birth for women over the age of 45 who wish to use their own eggs. Options such as adoption or IVF with egg donation may not be acceptable to women who wish to have genetically linked offspring and could involve various barriers including age.
Here comes the role of fertility preservation. At the moment, elective oocyte cryopreservation is the main option for protection against age-related fertility decline for women wishing to have biological children. The logic behind its use is that the success rates with ‘younger’ oocytes are better than after IVF in advanced age, and contrary to using donor oocytes, it may allow women to have genetically related offspring at an age where natural conception would be unlikely. However, there is often lack of awareness in women of reproductive age around what this treatment actually involves, how they can access it, what it costs, the possible implications and the success rates [10]. Elective egg freezing is one of the most controversial aspects in the world of assisted reproductive technology (ART), receiving great scientific interest [11, 12] and public attention [13]. The debate starts from terminology and extends to the acceptance of this treatment which has been described both as ‘women’s emancipation’ and as ‘dangerous delusion’ [14, 15].

Aims and methods

Family planning and sexual education have traditionally focused on contraception and prevention of sexually transmitted diseases. A focus should now also be placed on fertility awareness and fertility preservation as women who pursue fertility at an advanced age are increasingly common. This manuscript aims to give an update on the existing evidence around elective oocyte cryopreservation regarding success rates, risks, costs and benefits, current status and regulation of this treatment. It also highlights the need for fertility education and evidence-based, individualized counselling.

A thorough electronic search was performed in PubMed, Medline, Embase and Cinahl databases to provide an update on the existing evidence around elective egg freezing from the start of databases to August 2020. The search terms included fertility preservation OR egg freezing OR oocyte cryopreservation OR oocyte vitrification OR slow freezing AND success rates OR regulation OR ART OR fertility OR social egg freezing and combinations. Relevant results were identified, and their references were hand searched. The MESH terms used were ‘cryopreservation’, ‘oocytes’, ‘freezing’ and ‘vitrification’. The websites of regulatory authorities overseeing ART treatments in different countries were explored. References from selected studies were cross-checked, and meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were also searched.

A glimpse of the past

The first pregnancy (twin) from a frozen-thawed oocyte was reported in 1986 [16]. The slow freezing technique was used for years but without great success [17] until vitrification was introduced and the first live birth was reported [18]. The advantage of vitrification over slow freezing is that it offers an ‘instant’, rapid freezing from liquid to glass state without permitting the formation of ice crystals which could destroy the delicate oocyte. The success rates were improved with vitrification [19–21], which is not only the current cryopreservation technique of choice [22], but also less time-consuming and more cost-effective than traditional methods. Intracytoplasmic sperm injection (ICSI) is used to overcome the hardening of the zona pellucida following cryopreservation [23] and results in fertilization rates of 70–80% [24]. Even though cryopreservation impacts on the mitotic spindle essentially causing its destruction, this is reversed within a few hours after thawing, and embryo chromosomal abnormalities are not increased [25–27]. The technique appears to be safe and to double success rates [28]. Oocyte survival rates from the freezing-thawing process are reported as higher than 90% on average [29] leading to a sharp increase in the popularity of egg freezing.

In 2004, the European Society of Human Reproduction and Embryology (ESHRE) taskforce on Ethics and Law [30] looked into ethical considerations and reasons for gamete cryopreservation—preserving fertility after cancer, chronic illness, iatrogenic complications of treatment or simply with advancing age. In 2013, it was recognized that success rates with oocyte cryopreservation were as good as with fresh oocytes, and the experimental label on the technique was lifted with an ASRM (American Society for Reproductive Medicine) statement, and the American Society of Clinical Oncology also updated the guidance on fertility preservation [31, 32]. It was, however, highlighted that there was not enough evidence to support oocyte cryopreservation for the sole purpose of circumventing reproductive aging. Despite this statement, more than half the fertility units in the USA were already offering oocyte cryopreservation at the time, and most of them were also promoting it for non-medical reasons [33]. Thus, in 2014, in the reproductive facts section of the ASRM website, the idea of using oocyte cryopreservation without a medical indication was introduced, and relevant advice was offered. At the same time, the Canadian Fertility and Andrology Society released a position statement on egg freezing as an ‘option for women wishing to preserve their fertility in the face of anticipated decline’ [24]. Instead of thinking of oocyte cryopreservation as a ‘social’, ‘non-medically indicated’, lifestyle form of ART, Stoep et al. introduced the term ‘oocyte banking for anticipated gamete exhaustion’ introducing it as a preventative measure against future age-related infertility [34], while the ESHRE Taskforce for Ethics and Law used the term ‘oocyte cryopreservation for age-related fertility loss’ [35].
Current status

Egg preservation cycles have been documented as the fastest growing fertility treatment in the UK, increasing by 10% per year. There was a 240% increase from 2013 to 2018. In Spain, egg freezing cycles for fertility preservation increased from 4% of total vitrification procedures to 22% in a 10-year period, as reported by a retrospective, observational multicenter study [36]. Similarly, in the USA, fertility preservation cycles increased from 9607 in 2017 to 13,275 in 2018 [37]. Developing countries are following similar trends [38].

Surveys on women choosing elective fertility preservation reveal that the vast majority proceed with egg freezing due to lack of a suitable partner [39–42]. While women in their 20s or early 30s consider that their career aspirations would be a reason to consider egg freezing [43, 44], for the majority of surveyed women who did freeze their eggs, their career was ‘not at all’ a factor which influenced their decision [41]. While career aspirations and financial parameters including childcare support or maternity leave can somehow be managed, finding the right partner is outside one’s control and can carry social stigma [45]. Avoiding ‘panic partnering’ and future feelings of blame and guilt are amongst women’s incentives when considering fertility preservation [46]. Also, a percentage of patients who seek ovarian cryopreservation consider it protective against future medical issues that might be fertility impairing [39].

Evidence suggests that following egg freezing, very few patients regret their decision, and the majority of patients perceive the experience as empowering and would recommend it to others [40, 41, 47, 48]. A single US study reported that 49% of patients experienced mild/moderate regret which, however, seems to be associated with the information and emotional support received during the decision process and with perceived chances of live birth [49]. The most recent study concluded that 91% of patients reported no regret even if pregnancy was achieved without having to use the stored oocytes [41]. Half of the patients surveyed in this study had conceived naturally.

- Fertility awareness

Several studies demonstrate a lack of awareness on how age impacts fertility for women [40, 43, 50–52]. For fertility preservation, the main prognostic factor for success rates is the age at egg freezing. The best results are achieved if eggs are cryopreserved before 36 years of age according to a meta-analysis [53]. A woman wishing to become pregnant in her 40s with her own fresh eggs has a 6.6% estimated success rate, but if she had frozen her eggs at the age of 30, the success rate would jump to >40% per transfer [15]. However, most patients proceed with cryopreservation at the age of 36–39, with the mean age at the time of freezing being 37–38 and 80% of patients being above 35 [39–41, 54–56]. It is worth mentioning that the majority of surveyed women who had egg freezing wish they had done it earlier on, and only a minority received information regarding this treatment from their gynaecologist [40, 47]. Interestingly 42% of surveyed women who had elective egg freezing underestimated their chances of having a livebirth [41].

A US study on the attitudes of obstetric and gynaecology residents revealed that while the majority felt that age-related fertility decline should be discussed with patients at routine visits, most would not support the option of elective oocyte cryopreservation. Also, nearly half underestimated the effect of age on fertility, and 78.4% overestimated ART success rates [57]. Similarly, a survey including 5000 ACOG (American College of Obstetricians and Gynecologists) members concluded that due to limited consultation time and lack of knowledge, less than one-third of clinicians counsel patients regarding reproductive aging and fertility reservation [58]. Reproductive-aged women often resort to online sources to get information, and physicians are not exempt; they are also influenced by information found online including social media [59, 60]. Health professionals, from all specialties and from various stages of training, due to work demands are possibly more likely to postpone parenthood, hence good candidates for fertility preservation. However, a recent study showed that the majority of surveyed childless physicians of reproductive age had lack of knowledge regarding ART and fertility preservation options and expressed regret about not proceeding with fertility preservation in the past [61].

- Success rates

Reported success rates vary between different centres, and the capabilities of the technique are often ‘oversold’ or underestimated [64]. The results of a systematic review and meta-analysis are awaited [65]. Most evidence is based on egg freezing cycles for egg donation or for medical reasons, and data cannot always be extrapolated to women who seek elective fertility preservation. Although success rates have improved with the introduction of vitrification, in around four in five cases, the egg freezing treatment is unsuccessful according to 2017 HFEA (Human Fertilization and Embryology Authority) data [66].
The age at the time of freezing and the number of stored oocytes are the key factors that determine outcomes [67–69]. It is estimated that on average, 20 oocytes are required to achieve a pregnancy with the minimum proposed number being eight to ten [67, 68, 70]. However, for a given age, success rates will reach a plateau which cannot be surpassed regardless of oocyte number. Data from a multicenter retrospective study in Spain, the largest series to date, yielded interesting results [36]. The cumulative probability of live birth rate in the most optimistic scenario was reported as high as 94.4%, but this was limited for women who electively froze their eggs at 35 years of age or younger with 24 oocytes in storage. For 10 oocytes in storage, the cumulative live birth rate in this age group was 42.8%. For women who cryopreserved oocytes at an older age, the success rate was markedly lower reaching 5.9% for 5 oocytes and 17.3% for 8 oocytes. This means that one cycle may not be enough, but women are often willing to undergo multiple cycles to achieve a sufficient number of oocytes to be stored [71]. These data clearly suggest that age is the main factor that dictates success rates, and even with the most optimistic predictions, a live birth cannot be guaranteed.

Doyle et al. (2016) introduced ‘vitrified oocyte to live-born child efficiency’ to describe the ability of a frozen-thawed oocyte to result in live birth as a tool to guide decision-making regarding success rates and to indicate the number of oocytes (and therefore cycles) needed [69]. The authors suggest that this model may allow accurate estimations of the chance of having 1–3 children based on age at the time of egg freezing and the number of oocytes retrieved. It was estimated that 15–20 stored mature eggs were required for women younger than 38 for a 75% chance of having one child, whereas in the age group 38–40, 25–30 oocytes were needed for a 70% chance. Women above 42 would need 61 eggs to achieve such success rates. Although less efficient for women above 40, there was still a maximum 50% chance of a live birth with 30 stored oocytes (which would be challenging to achieve at this age group). Similarly, in another approach, Goldman et al. (2017) extrapolating data from ICSI cycles attempted to develop a user-friendly counselling tool to predict how many cycles would be needed and the probability of a woman having at least one, two or three live birth(s) [72]. These evidence-based tools can be adjusted taking into consideration parameters both related to patient characteristics and the unit’s expertise.

- Cost-effectiveness

The cost-effectiveness of elective oocyte cryopreservation is also controversial. Some studies conclude that since stored gametes may never need to be used, egg freezing may not be cost-effective compared to trying naturally or resort to standard IVF if needed [73, 74]. When freezing eggs at a young age such as in their 20s or early 30s, women may achieve better success rates but are more likely to pay more for storage and to conceive naturally as they have many reproductive years ahead. Thus, they may undergo the physical and emotional stress of treatment for no reason [75]. However, when freezing eggs at an advanced age, women may need more cycles and more oocytes in order to achieve comparable or worse success rates. In a large published series, the percentage of women returning to use their cryopreserved oocytes was only 12.1% [36].

Nevertheless, it has been demonstrated that, depending on age, egg freezing could represent better ‘value for money’ compared to conventional IVF [76, 77]. The authors conclude that it is cost-effective to freeze eggs up to the age of 37. This age may be best in terms of cost-effectiveness with a cost of $28,759 per additional live birth. The highest live birth rates are documented for ages below 34, but egg freezing still improved success rates up to the age of 40 [77, 78]. Freezing 16 eggs at age 35 reduced the cost per live birth by 27% while also increasing by almost 20% the odds of live birth. For women wishing to defer pregnancy until the age of 40, a lower overall cost per live birth was documented if they resorted to egg freezing before the age of 38 [77]. Since multiple factors are involved, maybe the answer regarding cost-efficiency should not be seen as a mathematical, common approach to all but should rather be tailored to the woman’s personal circumstances and characteristics. Response to stimulation, ovarian reserve and the number of children the woman wishes to have all matter in her decision-making [55]. Egg freezing has also been seen as an insurance policy. Using a parallel with health insurance, people set this up although the ideal scenario is not needing to use it [15]. It is important to note that existing data on the number of women returning to use their stored oocytes are preliminary since more women may return in the future.

- Regulation and funding

Uniform regulation regarding ART treatment is lacking even amongst European countries and sometimes within the same country [79]. This is not surprising as there are differences in terms of social, cultural and religious beliefs as well as the economic status and healthcare services. While most countries have relevant legislation, substantial heterogeneity is documented. Acceptance and regulation of the technique significantly differ amongst different countries. Existing differences in costs, legislation and storage limits, often result in fertility tourism.

According to the most recent ESHRE data, medically indicated fertility preservation is allowed in all 43 surveyed countries, but elective oocyte freezing is not permitted in Austria, France, Hungary, Lithuania, Malta, Norway, Serbia and Slovenia and is also not performed in Bosnia and

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Herzegovina and Moldova despite the absence of legislation that outlaws the technique [79]. While egg freezing cycles are increasing in Europe, few countries collect data regarding treatment details and outcomes [80].

The time limit for storage varies between different countries and often can only be extended for medical reasons. The 10-year storage limit in the UK has been heavily criticized. Due to this policy, women may get the false impression that they should freeze their eggs at an age when the results would be inferior [81]. Their other options would be to prematurely decide to have their eggs fertilized for further storage of embryos or to transfer their stored oocytes to other countries. Not being able to store eggs for more than 10 years comes as a paradox since women are allowed to use donor eggs up to the age of 50. As it has been previously highlighted by other authors, there should be no reason to deny women treatment with their own eggs at a similar age [82]. In July 2020, the UK storage limit for frozen eggs, sperm and embryos was extended by two years in view of the Covid-19 pandemic.

There are often various socioeconomic and cultural reasons that lead to postponing parenthood, which are possibly linked to the decision to proceed with fertility preservation [83]. However, elective egg freezing is not funded by the state in any country to our knowledge. This creates inequalities in access to treatment and leads to ethically ambiguous commercial initiatives. For instance, women can be encouraged to donate eggs and receive free treatment in return. Also, several companies promote and sponsor egg freezing for their employees. This is considered as an insurance policy for working women allowing them to focus on career without having to think of the ticking clock of reproduction and may be improving gender work place equality while at the same time serving the company’s interests [84]. However, this initiative has been regarded with scepticism [85, 86]. Is the hidden promise valid that delaying motherhood for the sake of success in the workplace will not have a toll on fertility through fertility preservation? Will women feel obliged to use this technology just because it is offered or because there is a stigma in the workplace against women who choose to reproduce earlier in their careers? Or will they feel obliged to continue working in this company in return? Women (or their employers) who can afford it may achieve a boost in their reproductive life span when others cannot. For those who cannot afford this, is it fair to depend on egg freezing share schemes or to their employer in order to preserve their fertility?

A word of caution

Egg freezing is neither a guarantee of a live birth nor a panacea for the various socioeconomic, cultural and emotional challenges which may lead women to defer parenthood [83]. Also, it comes with the risks of any IVF treatment. Immediate risks related to ovarian stimulation and egg collection such as ovarian hyperstimulation syndrome, bleeding, infection or aesthetic complications are reported below 1% [87].

Since vitrification is amongst the new advancements in ART, there are no long-term follow-up studies, and most evidence consists of retrospective studies and case reports [88]. There is some evidence demonstrating the differential impact of both slow freezing and vitrification on the gene expression profile of human frozen-thawed oocytes compared to non-cryopreserved controls [89]. The time in storage does not seem to affect the cycle outcome for either cryopreservation technique [29, 90, 91]. A retrospective cohort study [92] comparing outcomes of more than a thousand babies born from vitrified oocytes versus fresh oocytes suggested that oocyte vitrification does not increase adverse obstetric and perinatal outcomes nor congenital anomalies and complimented similar findings from previous smaller studies [28, 93, 94]. Of note, the proportion of female offspring was significantly higher in the vitrification group (53.8% vs. 47.4%). An observational study looked at outcomes following ART using frozen-thawed oocytes versus fresh oocytes in the same group of patients. Interestingly, 63 couples in this study had live births from both fresh and frozen oocytes with no significant differences in any of the investigated outcomes [95]. Outcomes should be monitored closely, and follow-up of the offspring should be warranted as for every technique which is not time tested [96]. Emphasis should be given in the long-term follow-up of the offspring to detect late manifestations of possible DNA damage including transgenerational effects.

The progress in ART technology has been rapid, often outstripping the speed of ethical debate. There is plethora of literature around the ethical aspects of fertility preservation. Elective egg freezing may provide women with false security. This sense of reproductive security could push the limits of childbearing age and could result in pregnancies not only in the 40s or early 50s but also in the 60s or 70s. Advanced maternal age is a recognized risk factor for various pregnancy complications, but women seem prepared to accept these risks [41]. Furthermore, the offspring will grow into a family where the mother is significantly older than the social norm, and this may create issues of adjustment. The number of single parent families by choice will possibly increase. However, these issues are shared with traditional IVF and egg donation [97], most countries have regulation regarding age limits in fertility treatment and current research does not suggest that women who proceed with elective fertility preservation have extreme reproductive goals. A retrospective cohort study, exploring attitudes and reproductive choices for women proceeding with fertility preservation, documented that the maximum age of parenthood they considered acceptable was below 44 years [47]. The results of another retrospective study on 1468 women who had elective egg freezing demonstrated that the 137 patients who returned to use their stored eggs did so, on average, at 2 years of storage, at an average age of 39.2 years [67, 68].
Since elective egg freezing is only possible in the private setting, commercialization is unavoidable [98], and clever promotion campaigns and media often create false hopes [99, 100]. Since there is no uniform reporting system, the information provided by websites and brochures may be selective. A study looking into IVF center websites found that performance was reported in 51 different ways [101]. Women should look into the clinics’ success rates for their own age group and should ask for live birth rates. It is important to know how much experience the unit has in vitrification and how many women came back to use their frozen eggs. Since more than one cycle may be required to achieve sufficient numbers, fertility units have created offer packages to cover the cost of the stimulation cycles and storage. However, maybe women should consider storing eggs in different units to eliminate unpredictable factors (not ‘putting all one’s eggs in one basket’ as per media cover titles).

The role of individualized counselling should be highlighted [102] in the context of a fertility team including clinicians, nurses and psychologists. Emotional support is a key especially since contrary to what happens in conventional IVF, women seeking egg freezing are most likely to go through this process alone. The fate of the stored oocytes in case these are not used or in case of illness or death and other unforeseen factors, such as possible human errors, unpaid storage fees, destruction or even theft, should also be touched on in the discussion, and decisions should be documented [103]. Age-specific success rates are also dependent on the number of oocytes stored; therefore, counselling should explain the possible need for multiple stimulation cycles [87].

**Future perspectives**

For women who want children, fertility education is key. Natural conception or donor insemination is the preferred way, and couples who have decided to have children should start trying early. For those, though, that conventional family planning is not possible due to various reasons, the chance for motherhood should not be denied, and they should be encouraged to be proactive to prevent infertility [104]. The aim should be to increase awareness amongst women of reproductive age regarding age-related fertility decline. Funding strategies could potentially be developed in the future to prevent infertility as preventative medicine has been developed in so many other fields. Also, algorithms could be developed to individually assess fertility status and cultivate a pro-fertility mentality in a realistic context [105]. The Fertility Assessment and Counseling Clinic in Denmark is a good example of such strategy offering tailored counselling with the aim to predict and protect fertility [106]. Half the women who attended this clinic wished to explore ways to preserve or optimize fertility, and 70% wanted to be informed regarding how long they could safely postpone childbearing.

The vast majority found this counselling useful, and 35% changed their decision to delay pregnancy.

There are multiple roads to parenthood, but at the moment, fertility preservation is the main approach to age-related fertility decline for women who want to have genetically related offspring. This may change in the near future since scientific developments never cease. Stem cell research is promising and rapidly evolving [107]. Somatic cells such as skin cells may be reprogrammed to serve as functional gametes [108]. Also, as our understanding increases in demystifying the physiology of reproduction and stem cells are identified within the ovary, perhaps there will even be the possibility to pause the ovarian biological clock and prevent follicle atresia [109–111].

Should we, as a society, be moving towards making egg freezing a common procedure? Should the gift to our daughters’ graduation be fertility preservation? Many questions around fertility preservation still remain unanswered, and more well-designed studies are needed before reaching sound conclusions. However, women today do have this option which was not available in the past. Elective egg freezing should not be seen as a means to intentionally delay parenthood but rather as a preventative measure to preserve fertility. Fertility preservation should be included in the discussion around reproductive options in order to ensure informed decisions.

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**Compliance with ethical standards**

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