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OPINION

Age-related fertility decline: is there a role for elective ovarian tissue cryopreservation?

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ABSTRACT: Age-related fertility decline (ARFD) is a prevalent concern amongst western cultures due to the increasing age of first-time motherhood. Elective oocyte and embryo cryopreservation remain the most established methods of fertility preservation, providing women the opportunity of reproductive autonomy to preserve their fertility and extend their childbearing years to prevent involuntary childlessness. Whilst ovarian cortex cryopreservation has been used to preserve reproductive potential in women for medical reasons, such as in pre- or peripubertal girls undergoing gonadotoxic chemotherapy, it has not yet been considered in the context of ARFD. As artificial reproductive technology (ART) and surgical methods of fertility preservation continue to evolve, it is a judicious time to review current evidence and consider alternative options for women wishing to delay their fertility. This article critically appraises elective oocyte cryopreservation as an option for women who use it to mitigate the risk of ARFD and introduces the prospect of elective ovarian cortex cryopreservation as an alternative.

Key words: age-related fertility decline / elective oocyte cryopreservation / ovarian tissue cryopreservation / fertility preservation / vitrification

Introduction

Over the last 50 years, societal perceptions and cultural reproductive norms have evolved significantly. The development of gender equality and improved women's rights have enhanced professional and educational opportunities, financial independence and empowerment for women. This has resulted in a shift of reproductive aspirations and plans, as exemplified by the increasing age of first-time motherhood observed amongst women in the European Union (EU), from 28.8 years old in 2013 to 29.3 in 2018 (Eurostat, 2020). This deferment of childbearing years has significant reproductive implications. The progressive reduction in number of primordial follicles causes depletion of ovarian reserve in an exponential fashion from the age of 37 years onwards (Devesa *et al.*, 2018). This results not only in a reduction in quantity of oocytes but also a deterioration in oocyte quality, thereby potentiating risk of aneuploidy (Hassold and Hunt, 2001). Clinically, this exhibits itself as reduced fecundity and an increased risk of miscarriage; from 10% in the second decade of life, to 53% in those over 45 years old (Magnus *et al.*, 2019). Advanced age is also associated with an increased incidence of uterine pathology, including adenomyosis, commonly observed in women aged 40–49 years old (Naftalin *et al.*, 2012) and leiomyomas, which are associated with unfavourable reproductive outcomes and increased obstetric complications (Olive and Pritts, 2010). Delaying motherhood thereby, results in inevitable

and often untreatable age-related consequences, which if not pre-empted and actioned, may result in involuntary childlessness, or an inability to meet reproductive aspirations. It is therefore unsurprising that as the age of first-time motherhood has increased, microsimulation models used to estimate the rates of permanent involuntary childlessness amongst six European countries, have demonstrated that overall rates have doubled since the 1970's, with an increase of 2.5% observed in Sweden, 3% in Austria, Netherlands, Czech Republic and West Germany and 4% in Spain (Te Velde *et al.*, 2012). Furthermore, the risk of involuntary childlessness in women aged over 40 years is 3% higher than in women under 30 years old (33% versus 36%, respectively) (Steenhof and De Jong, 2000; Te Velde *et al.*, 2012). Advancements in artifical reproductive technology (ART) have provided women the opportunity to overcome such challenges by utilizing oocyte donation for in vitro fertilisation (IVF) cycles. Although this enables the experience of gestation, it denies the opportunity for biologically related offspring. Women wishing to preserve their fertility to mitigate the impact of age-related fertility decline (ARFD) can now undergo elective oocyte cryopreservation (EOC). Whilst this allows women the opportunity to extend their reproductive years, it does not guarantee future livebirths. Whilst ovarian cortex cryopreservation has been used to preserve reproductive potential in women for medical reasons, such as undergoing gonadotoxic chemotherapy, it has not yet been used in the context of ARFD. The aim of this article is to critically appraise EOC as an option for women wishing to preserve their fertility to prevent ARFD and to introduce the prospect of elective ovarian cortex cryopreservation as an alternative.

Elective oocyte cryopreservation

Oocyte cryopreservation (OC) was first undertaken in the late 1980s, using a slow freeze and rapid thaw technique (Chen, 1986). However, poor success rates were observed initially due to the challenges associated with the slow freezing process. These included technical barriers, such as the high rate of ice crystal formation and disruption caused to the structural stability of the microfilaments (Pickering and Johnson, 1987), with a subsequent impairment of chromosomal segregation and hardening of the zona pellucida, which contributed to low fertilization rates (Vincent *et al.*, 1990). The subsequent development of oocyte vitrification, which involved ultra-rapid cooling methods, through the process of vitrification to produce a non-crystalline amorphous solid, proved to be a faster technique with superior outcomes (Smith *et al.*, 2010). Through vitrification, damage caused to the internal structures within the oocyte could be minimalized, thereby overcoming the barriers surrounding the hardening of the zona pellucida (Fabbri *et al.*, 1998). Technological advancements have since improved oocyte survival and reproductive outcomes (Smith *et al.*, 2010), with similar implantation, pregnancy, miscarriage and livebirth rates (LBRs) demonstrated between fresh and cryopreserved oocytes (Cobo *et al.*, 2010; Crawford *et al.*, 2017). This is exemplified by the fact only 20 vitrified oocytes are now required to achieve a pregnancy (Cobo *et al.*, 2013), compared to the estimate of 100 oocytes previously (Porcu, 1999). Consequently, oocyte vitrification has enabled women the opportunity to preserve their reproductive potential by cryopreserving oocytes prior to the physiological decline in quantity and quality; referred to herein as EOC. The most prevalent indication for women to consider EOC has been consistently identified as not having a partner, although less prevalent reasons are career or education related (Baldwin, 2019; Baldwin *et al.*, 2019; Jones *et al.*, 2020a).

EOC has previously been subject to criticism, with suggestions that it steers women into a false sense of hope regarding their future fertility, leading to delays in attempting conception and increased anxiety (Mertes, 2015; Zoll *et al.*, 2015), characterizing the need for individualized, comprehensive and realistic counselling regarding future outcomes. Furthermore, storage of a finite number of oocytes does not guarantee future offspring; it merely offers an opportunity, which may be limited by loss during thaw or future unsuccessful cycles. This is exemplified by data showing oocyte thaw survival rates between 80% and 90%, and fertilization rates following intracytoplasmic sperm injection (ICSI) between 70% and 80% (Saumet *et al.*, 2018).

As the process is still novel, only 3.1–12.1% of women who have undergone the procedure have since returned to use their cryopreserved oocytes (Ben-Rafael, 2018; Cobo *et al.*, 2018; Gürtin *et al.*, 2019; Kasaven *et al.*, 2020). Consequently, successful LBRs of 17.5–30.5% have been observed in such women (Gürtin *et al.*, 2019; Kasaven *et al.*, 2020), highlighting that EOC is a feasible method of fertility preservation for ARFD. The chances of successful livebirth are dependent on two factors; age at the time of cryopreservation and the number of oocytes retrieved. It has been suggested that between 20 and 25 oocytes are required for an 80–85% chance of livebirth in a woman of 35 years old (Cobo *et al.*, 2015). A further study highlighted that a 35-year-old woman would need to undergo an average of 1.2 cycles to preserve at least 16 meiosis stage II (MII) mature oocytes, for two future potential thaw cycles (Devine *et al.*, 2015). Further recommendations suggest that women <38 years should cryopreserve between 15 and 20 MII oocytes for a 70–80% chance of at least one livebirth and 25–30 MII oocytes in women aged 38–40 years for a 65–75% chance (Doyle *et al.*, 2016). Finally, a proposed model predicting the likelihood of livebirth for EOC when stratifying for age, demonstrated that if women aged 34, 37 and 42 years old cryopreserved 20 mature oocytes each, a 90%, 75% and 37% likelihood of having one livebirth would be expected, respectively (Goldman *et al.*, 2017). Thus, when considering the average number of oocytes retrieved per cycle is 12 (Ben-Rafael, 2018), more than one cycle of ovarian stimulation is often required to achieve a favourable chance of livebirth.

The mean age at which women underwent EOC in one of the largest studies thus far was 37.7 years old (Cobo *et al.*, 2016). However, evidence suggests this is perhaps too late to optimize the chances of successful livebirth. Especially considering women ≤35 years old were reported to have an LBR of 68.8%, compared to 42.1% when >35 years old (Cobo *et al.*, 2018). This is consistent with a meta-analysis, with success rates from both slow freezing and vitrification cycles declining after the age of 36 years old (Cil *et al.*, 2013). Further data from 128 autologous IVF treatment cycles, deduced that the efficiency per warmed oocyte, directly correlating to one successful livebirth in the following age groups at the time of cryopreservation were as follows: 7.4% when <30, 7.0% when 30–34, 6.5% when 35–37, 5.2% when ≥38 and 6.8% when 41–42 (Doyle *et al.*, 2016). Overall, the age-associated oocyte to child efficiency was described as 6.7% (Doyle *et al.*, 2016). Moreover, reproductive outcomes were better in women ≤35 years old at the time of oocyte cryopreservation, when

compared with those above >35 years old (50% (95% CI 32.7–67.3) versus 22.9% (95% CI 14.9–30.9)) (Cobo *et al.*, 2016). Further evidence suggests the overall percentage of positive outcomes, including successful livebirths or ongoing pregnancies, declines significantly when age of cryopreservation increases beyond 40 years (Gürtin *et al.*, 2019). As awareness of fertility and EOC increases, as exemplified by a study of 973 women, whereby 83% of the cohort had heard of the procedure (Lallemant *et al.*, 2016), it is anticipated women will undergo EOC at earlier ages in the future. However, from an economic perspective, it has been shown to not be cost-effective for a 25-year-old healthy woman to undergo EOC with the intention to delay childbearing until the age of 40, primarily because the chances of conception are higher and the likelihood of the preserved oocytes being used is lower (Hirshfeld-Cytron *et al.*, 2012). Thus, cost-effective analyses suggest the optimal age to undergo oocyte freezing is 35 years old, based on a probability of returning to use the stored oocytes of >61% and the willingness to spend approximately €19 560 per livebirth (Van Loendersloot *et al.*, 2011).

Despite the inferior outcomes associated with increased age, the majority of women undergoing EOC do not regret undergoing the process, with many perceiving the procedure as an 'insurance' against infertility (Stoop *et al.*, 2011, 2015; Jones *et al.*, 2020a). Where regret is experienced, it is most commonly attributed to the associated financial expense (Jones *et al.*, 2020b), or low numbers of oocytes cryopreserved (Greenwood *et al.*, 2018).

Many studies have assessed the efficacy and safety of OC with respect to embryonic and foetal outcomes, whereby the duration of cryopreservation does not appear to have negative implications on the risk of aneuploidy (Forman *et al.*, 2012; Goldman *et al.*, 2015), nor does it alter the gene expression profiles of the thawed oocytes (Stigliani *et al.*, 2015). In addition, there are no apparent increased obstetric or perinatal risks associated with pregnancies using cryopreserved oocytes (Cobo *et al.*, 2014). In a study of 200 infants, the incidence of congenital abnormalities (2.5%) was similar in those born through oocyte vitrification to those from spontaneous conception (Chian *et al.*, 2008).

One of the limitations of EOC includes the requirement to undergo controlled ovarian stimulation (COS) and IVF to achieve pregnancy (Table I). Ovarian stimulation performed in women with infertility, has been associated with both short-term psychological health issues and longer-term episodes of depression and feelings of poor self-image (Brod *et al.*, 2009). Furthermore, one study demonstrated that more than 50% of infertile women undergoing COS, reported it impacted their daily life, and almost a third felt the daily injections restricted their everyday activities (Huisman *et al.*, 2009). Conversely, however, a study evaluating the fertility quality of life (FertiQol) treatment score amongst women who have undergone EOC, demonstrated that there was no significant difference in treatment scores between women who underwent longer periods of COS to those with shorter stimulation cycles (Jones *et al.*, 2020b). A potential medical risk factor from COS includes the risk of ovarian hyperstimulation syndrome. Whilst the risk is small, following the implementation of GnRH agonist triggers (Kol and Humaidan, 2013), it may be increased in women undergoing EOC, by virtue of their younger age and higher ovarian reserve (Delvigne, 2017). Other controversial risk factors include the associated risks of borderline ovarian tumours (BOTs) or gynaecological malignancy. In one of the largest longitudinal cohort studies including a 15-year follow-up of over 19 000 women receiving IVF, the risk of BOT was significantly increased amongst the IVF group, compared to the general population (van Leeuwen *et al.*, 2011). This is consistent with a recent systematic review which confirmed that BOTs are significantly associated with fertility treatment (Barcroft *et al.*, 2021). The risk of invasive ovarian cancer associated with fertility treatment is less consistent. In subgroup analyses, an observed increased incidence amongst IVF groups has been demonstrated (van Leeuwen *et al.*, 2011; Barcroft *et al.*, 2021), although other studies have also not identified a significant association (Cobo *et al.*, 2016). Interestingly, the incidence of cervical and breast cancer is significantly lower in IVF treatment subgroups when compared with those who have not undergone IVF (Barcroft *et al.*, 2021). Although such relationships are observed, an association does not necessarily imply causality, and as evidence remains conflicting, it is difficult to attribute such relationships to the process of IVF. Furthermore, it should be emphasized that the evidence presented has been extrapolated from a population of infertile women, and therefore may not be applicable to the cohort of healthy women undergoing COS for the purposes of ARFD. Moreover, other confounding factors should also be considered. For example, by virtue of their inability to conceive, women undergoing IVF may differ in respect to risk factors for such malignancies, as the protective physiological processes of pregnancy and breastfeeding are absent. Also, ovarian stimulation protocols included in earlier studies may have been more aggressive than the controlled modern regimens now utilized. Evidently, it is important to continue longitudinal follow-up of women undergoing EOC, in order to establish whether similar relationships can be deduced amongst this cohort.

Ovarian tissue cryopreservation

An alternative method of fertility preservation for ARFD is ovarian tissue cryopreservation (OTC) (Martinez, 2017). OTC involves laparoscopic resection of ovarian tissue, either from the ovarian cortex containing primordial follicles or whole ovary; followed by cryopreservation (Salama and Woodruff, 2015). The concept was proposed initially to mitigate the risk of secondary premature ovarian insufficiency (POI) in women undergoing gonadotoxic chemotherapy and to preserve fertility in pre- and peripubertal girls, in whom OC is not possible (Salama and Woodruff, 2015; Jensen *et al.*, 2017b). Figures from national databases suggest that based on a population of 500 million in the European Union, between 2500 and 6500 OTC procedures take place in Europe per year (Van der Ven *et al.*, 2016). Given the increasing use and acceptance, it is no longer considered experimental in patients at risk of iatrogenic ovarian failure according to criteria by the European Society of Human Reproduction and Embryology (ESHRE) (Provoost *et al.*, 2014). Following the success of OTC as an established method of fertility preservation in women with cancer, it has evolved further as a technique for women undergoing treatment with a high or intermediate risk of POI due to benign conditions (Jadoul *et al.*, 2017; Lotz *et al.*, 2019). This includes autoimmune, haematological or medical illness treated by cytotoxic agents, presence of bilateral ovarian tumours and severe recurrent ovarian endometriosis (Jadoul *et al.*, 2017; Lotz *et al.*, 2019).

Multiple centres have performed frozen-thawed orthotopic ovarian tissue transplantation worldwide. The thawed or warmed tissue is

Table I Advantages and disadvantages of elective oocyte cryopreservation versus elective ovarian tissue cryopreservation.

	Elective oocyte cryopreservation	Elective ovarian tissue cryopreservation
Advantages	• Biological offspring is feasible • Invasive surgery and general anaesthesia is not required • Oocytes retain their reproductive potential from the age they were cryopreserved, with improved outcomes observed in younger women • Similar outcomes between cryopreserved warmed oocytes and fresh IVF cycles • Procedure is cost-effective when cryopreservation is carried out at the optimal age • Successful pregnancy, livebirth and perinatal outcomes have been reported • Duration of cryopreserved oocytes does not affect the risk of aneuploidy or alter gene expression of the thawed oocytes • Procedure is associated with a low rate (%) of decision regret	• Biological offspring is feasible • Hundreds of primordial follicles can be cryopreserved at one time • Follicles within the ovarian tissue retain their reproductive potential from the age they were cryopreserved, with improved outcomes observed in younger women • Effective methods have been described to improve follicular survival rates • Successful outcomes have been reported regarding endocrine function, livebirth, pregnancy rates and perinatal outcomes • Spontaneous conception is possible • Several pregnancies can be achieved from the same graft • Women can use cryopreserved tissue later in life as a method of cHRT to prevent POI or early menopause, if not used for fertility preservation for ARFD
Disadvantages	• Offspring is not guaranteed • More than one cycle of COS may be required to retrieve adequate oocyte numbers to improve chances of successful livebirth • Ovarian stimulation increases the risk (albeit minimal) of thrombotic events and OHSS • Undergoing ovarian stimulation is associated with short and long-term psychological effects in infertile couples • Poor outcomes including total number of oocytes retrieved, pregnancy and livebirth rates are associated in women undergoing the procedure >35 years old • Oocytes may not end up being used, due to spontaneous conception, or through choice • A finite number of oocytes are retrieved and cryopreserved	• Offspring is not guaranteed • Multiple laparoscopies are indicated (resection and implantation of ovarian tissue) with associated surgical and anaesthetic risk • Long-term surgical risks such as adhesions, could impair the ability to achieve spontaneous pregnancy • Risks are associated with poor longevity of the graft when cryopreservation is performed at an advanced age or an inadequate volume of tissue is retrieved • Poor outcomes including pregnancy and livebirth rates are associated in women undergoing the procedure >40 years old • Tissue may not end up being used, due to spontaneous conception, or through choice • Risk of removing ovarian tissue may impact ovarian reserve and bring age of menopause earlier

ARFD, age-related fertility decline; COS, controlled ovarian stimulation; cHRT, cell tissue hormonal replacement therapy; OHSS, ovarian hyperstimulation syndrome; POI, premature ovarian insufficiency.

transplanted into either the broad ligament, the remaining ovary or ovarian fossae (Jensen *et al.*, 2017a). Following transplantation, restoration of endocrine function is dependent upon various factors at the time of OTC, including the age of the woman, the follicular density and quality of the graft tissue (Takae and Suzuki, 2019). The procedure is deemed successful when both return of menstruation and follicular growth is observed. A recent meta-analysis highlighted that ovarian endocrine function was restored in 85.2% (n = 309) of women receiving transplanted tissue (Pacheco and Oktay, 2017), and in a separate study of 800 women, amongst 44 women who underwent ovarian tissue reimplantation following retrieval, 98% (n = 43) had resumed or improved ovarian function (Diaz-Garcia *et al.*, 2018). Reasons for unsuccessful return of ovarian function have been reported as inadequate quantity of ovarian tissue cryopreserved, or when the procedure was performed at an advanced age (Pacheco and Oktay, 2017). The mean duration of ovarian function has been demonstrated to be 5 years, although normal graft function can be maintained up to 10 years later (Donnez *et al.*, 2015; Takae and Suzuki, 2019). In addition, outcomes have been shown to be similar between both fresh and frozen grafts, with comparable ovarian function observed after 2 years of follow-up (Silber *et al.*, 2015; Sheshpari *et al.*, 2019).

The pregnancy rate following orthotopic transplantation was reportedly between 27% and 37% (Bedaiwy *et al.*, 2008; Jensen *et al.*, 2015; Silber, 2016; Van der Ven *et al.*, 2016) compared to 26% in a study of 285 women who underwent frozen-thawed ovarian tissue transplantation. (Dolmans *et al.*, 2021). As the method of cryopreservation and surgical techniques have been optimized (Beckmann *et al.*, 2019), more recent reports from three major centres from Tel Aviv, Brussels and St Louis have published pregnancy rates of 50% and LBRs of 41% amongst a cohort of 60 patients (Shapira *et al.*, 2020). Much like OC, the ovarian reserve and genetic quality of the oocyte is dependent on the age at the time of cryopreservation, and thus an independent

predictive factor for pregnancy (Rozen *et al.*, 2021), with the highest success rates observed in women aged 34 years or younger (Lotz *et al.*, 2019). Further data suggests that the pregnancy rate when OTC was performed at the following ages: <30, 30–34, 35–39 and >40 years old, were 41%, 33%, 18% and 0%, respectively (Van der Ven *et al.*, 2016). These findings are also consistent with data from one of the largest national fertility databases, which deduced that OTC should only be performed in women ≤40 years old (Beckmann *et al.*, 2018).

Various studies also report a LBR between 21.6% and 30% amongst women undergoing OTC (Dolmans *et al.*, 2009; Andersen, 2015; Lotz *et al.*, 2016; Meirow *et al.*, 2016; Van der Ven *et al.*, 2016). An overall trend for lower LBRs associated with OTC may be attributed to the impaired folliculogenesis observed, causing disruption between the granulosa cells and oocytes, subsequently resulting in reduced oocyte maturity, poor fertilization rates and inadequate embryo quality (Dolmans *et al.*, 2009). However, as with most novel therapies, it is expected that further advancement will improve outcomes, particularly as novel cryopreservation regimens are developed.

Although literature reports more than 130 livebirths following OTC since 2017 (Donnez and Dolmans, 2017; Lotz *et al.*, 2019; Oktay *et al.*, 2021), the figure is now likely to be more than 200 (Dolmans *et al.*, 2020). The largest systematic review of 210 recipients reported that 70% of all pregnancies were achieved spontaneously (n = 84), whereas 30% (n = 36) were following IVF (Sheshpari *et al.*, 2019). Furthermore, in a study of 285 women; from 106 who conceived, 63% (n = 67) did so naturally whilst 37% (n = 39) conceived through IVF (Dolmans *et al.*, 2021). Women can also achieve multiple pregnancies from the same graft, with some cases reporting >3 pregnancies in the same woman (Jensen *et al.*, 2015). Data extrapolated from various national databases suggests that the majority of pregnancies following OTC were carried to term with positive perinatal outcomes (Pacheco and Oktay, 2017; Jensen *et al.*, 2017a). A congenital abnormality rate of 1.2% has been reported, which is comparable to the general population (Pacheco and Oktay, 2017). It is important to consider that the majority of data regarding reproductive outcomes following ovarian tissue transplantation were taken from women who had undergone chemotherapy or radiotherapy for malignant pathology or had POI (78% versus 20%, respectively); and therefore likely had an existing degree of ovarian insufficiency prior to transplantation (Sheshpari *et al.*, 2019).

For the purpose of fertility preservation, the number of follicles restored during the freeze-thaw stage is important (Rozen et al., 2021), and for that to be achieved, at least one-half to two-thirds of the ovarian cortex is usually harvested (Meirow, 2008). In such instances, a follicle survival rate as high as 84% from frozen-thawed tissue has been described (Kristensen *et al.*, 2018), and a follicular density of 89% has been retained following implantation of paired fresh samples (Christianson *et al.*, 2021). One of the current challenges of OTC is optimizing survival of the follicular pool within the ovarian graft. Significant follicle demise occurs secondary to the exposure of hypoxia. Transplantation onto the vascular pelvic structures, is dependent on the process of neovascularization which occurs during the first 10 days post-implantation (Li *et al.*, 2014). Inadequate neovascularization results in oxygen-derived free radicals and lipid peroxidation, which triggers ischaemic reperfusion injury within the ovarian tissue (Takae and Suzuki, 2019). The initial phase of ischaemia can be associated with loss of the follicular reserve by up to 60%, which can subsequently impact ovarian reserve and longevity of the graft (Kim *et al.*, 2004; Gavish *et al.*, 2014; Oktay *et al.*, 2021). Various methods have been described to reduce the risk of post-implantation graft hypoxia, such as using the isoform of vascular endothelial growth factor 165 within a collagen matrix to encapsulate the ovarian tissue (Henry *et al.*, 2015). This has been demonstrated to result in earlier revascularization and improved angiogenesis of the graft in the first 3 days post-implantation (Henry *et al.*, 2015). Furthermore, anti-apoptotic agents such as Sphingosine-1-phosphate (S1P), an endogenous phospholipid messenger, significantly accelerates revascularization of the ovarian grafts to 2–3 days and doubles the microvascular density (Li *et al.*, 2014). This results in reduced tissue hypoxia and apoptosis of follicular cells, thus improving overall success of the transplantation (Soleimani *et al.*, 2011). Plasma levels of S1P are significantly higher in younger women and synthesis has been shown to be directly associated with oestrogen levels (Guo *et al.*, 2014). Therefore, if elective OTC (EOTC) is undertaken in young healthy women, improved outcomes and greater graft longevity could potentially be observed, when compared with women who have undergone the procedure for medical pathology.

A second cause of follicular demise is the process of cryopreservation itself, which promotes uncontrolled follicular activation of primordial follicles, also known as *follicular burnout* (Masciangelo *et al.*, 2019). The administration of recombinant anti-Müllerian hormone, has been shown to inhibit initiation of primordial follicle recruitment in mice studies, which prevents ovarian reserve depletion and subsequent follicular burnout (Kano *et al.*, 2017). Further animal studies have proposed the use of adipose-derived stem cells, whereby a mean survival rate of 62% was reported one week following transplantation (Manavella *et al.*, 2018). Moreover, the application of microsurgical scissors has been shown to preserve the total number of follicles, but to the detriment of triggering follicular abnormalities including stromal death (Herraiz *et al.*, 2020). During the process of vitrification, solutions consisting of a high concentration of cryoprotectant agents (CPAs) and high viscosity are used in order to protect the tissue and cells from dehydration or changes in temperature (Leonel *et al.*, 2019; Shahsavari *et al.*, 2020). The most commonly used CPA's in vitrification of ovarian tissue includes dimethyl sulfoxide (DMSO), ethylene glycol (EG), sucrose and 1-2-propanediol (PrOH) (Leonel *et al.*, 2019). However, when used for a prolonged period of time, detrimental impairment of the tissue can occur in addition to cytotoxicity. Studies suggest that enhanced outcomes with a survival of more than 90% intact follicles, can be achieved when a combination of DMSO in low concentration (27%) is used with EG and other CPAs (El Cury-Silva *et al.*, 2021). Even higher rates (98%) of normal follicles following cryopreservation are observed when a combination of 27% of EG and 27% glycerol are used with non-permeable synthetic polymers (El Cury-Silva *et al.*, 2021). Thus, it is feasible for vitrification techniques to preserve the integrity of the majority of follicles (El Cury-Silva *et al.*, 2021).

Elective ovarian tissue cryopreservation

For women who wish to preserve or extend their reproductive potential to prevent or restore their fertility following ARFD, EOTC may

offer an alternative option to EOC. Similar to the motives for undergoing EOC, women who do not plan on having children until a time when their reproductive potential has started to deteriorate could consider EOTC. Women with normal endocrine function and appropriate ovarian reserve would be suitable to undergo the procedure at a time when age and follicular density are optimal, following extensive counselling and with the understanding that outcomes will be related to age at EOTC. The same surgical technique should be used as is currently utilized for OTC for medical indications. Once the circumstances of women who choose to undergo EOTC change to an extent where conception is desired, if the remaining ovarian reserve has physiologically deteriorated, reimplantation of the cryopreserved ovarian tissue could be undertaken, thereby restoring or enhancing their reproductive potential.

Consideration of the potential risks and benefits is essential in such a novel approach. When evaluating the safety of OTC, primary risk includes undergoing at least two laparoscopic procedures; retrieval and implantation of ovarian tissue. The complication rate so far reported in 1302 women who underwent retrieval and implantation was 0.2% (n = 2) and 0.07% (n = 1), respectively (Beckmann *et al.*, 2018). A separate analysis of 476 women identified no cases of significant surgical adverse events (Dolmans *et al.*, 2013). Therefore, the overall surgical risks are similar, if not smaller, compared to laparoscopic surgery performed for other benign pathology (Lotz *et al.*, 2019). In a study of 90 women who underwent laparoscopic salpingo-ovariolysis, 40.2% developed moderate to severe adhesion reformation identified during early *second look* laparoscopy (Alborzi *et al.*, 2003). Whilst no correlation has been identified between self-reported pain, physical or emotional scores with the presence or absence of pelvic adhesions identified during diagnostic laparoscopy (Cheong *et al.*, 2018), adhesions are associated with increased risk of infertility (Vrijland *et al.*, 2003), which would be counterproductive in a procedure intended to preserve and restore reproductive potential.

In EOTC, iatrogenic POI is a risk factor following resection of substantial volumes of ovarian tissue. Therefore, individualized assessment including consideration of age and pre-existing ovarian reserve should be determined when deciding how much ovarian tissue to resect (Oktay *et al.*, 2021). Evidence suggests removal of <30% of ovarian tissue does not have a significant impact upon ovarian reserve (Vuković *et al.*, 2019). Data can also be extrapolated from outcomes following unilateral oophorectomy (UO); where in a study of more than 23 000 women, menopause was brought forward by only 1 year (Bjelland *et al.*, 2014). Another study demonstrated that when UO was performed at 20, 30 and 45 years of age, it was associated with onset of menopause at 44.7, 46.3 and 48.7 years old, respectively (Rosendahl *et al.*, 2017). In the eventuality of POI following EOTC, premature reimplantation could be undertaken, or alternatively hormone replacement therapy (HRT) used until reimplantation was considered at a time when conception was subsequently desired. Consideration is also required for the potential impact upon reproductive potential following EOTC. Data can be inferred from a study of women who underwent UO, whereby no impact on conception rates, both spontaneously and following assisted conception, was demonstrated (Lass, 1999).

When compared with EOC, EOTC offers a great advantage of the possibility of spontaneous conception. This is exemplified by a study comparing OTC with OC, whereby almost half of the OTC patients conceived naturally (Diaz-Garcia *et al.*, 2018). The potential for natural conception would likely have significant psychological, emotional and economic advantages, whilst reserving the option of IVF, if necessary. Although EOTC provides the opportunity for spontaneous conception, much like EOC, it may not guarantee future offspring, particularly as reproductive outcomes are also dependent on paternal factors, such as age. This is important considering the mean paternal age has also increased globally, from 27.4 to 30.9 years observed in America (Khandwala *et al.*, 2017; Bergh *et al.*, 2019), and from 29.2 in 1980 to 32.1 over the last four decades in England and Wales (Birth Statistics, 2007). In a recent systematic review, both the livebirth and pregnancy rate were increased when the male age was ≤40 years old in autologous oocyte cycles, and the miscarriage rate more likely when the male was >40 years old (Morris *et al.*, 2020). Paternal age should therefore also be considered in the management of ARFD.

Moreover, OTC provides the opportunity to preserve hundreds of primordial follicles at once (Lotz *et al.*, 2019), thereby not restricting women to a finite number of oocytes cryopreserved, which is a known limitation of EOC. Interestingly, a recent cost-analysis study of women undergoing onco-fertility treatment in America, demonstrated that OC was more costly than OTC ($16 588 versus $10 032, respectively) (Chung *et al.*, 2021). In a prospective study comparing the efficacy of oocyte vitrification vs OTC in women undergoing gonadotoxic treatments, higher LBRs per patient were observed in the OC group, although there was no statistical significance between the groups (32.6% versus 18.2%, respectively) (Diaz-Garcia *et al.*, 2018). Furthermore, a sensitivity analysis reported no successful pregnancies in women who underwent OTC above the age of 36, compared to a 30% pregnancy rate in women undergoing oocyte vitrification above the same age (Diaz-Garcia *et al.*, 2018).

Studies so far have reported an average storage time of 9.1 years, with an upper range of 17.9 years, which resulted in a 98% follicle survival rate following OTC (Kristensen *et al.*, 2018). Should EOTC therefore subsequently transcend into clinical practice, updated legislation is essential to ensure tissue is not implanted for fertility restoration purposes in women outside of their natural reproductive years. As such, limiting the age at reimplantation to a maximum of 45 years may be an appropriate compromise, although further ethical reflection and debate is needed. In addition, if a woman decides not to use her stored ovarian tissue to extend her reproductive potential, it could instead be used later in life to alleviate menopausal symptoms, as a method of cell tissue HRT (Kristensen and Andersen, 2018). If the tissue is used for this purpose, permanent contraception such as concomitant bilateral tubal occlusion would be essential, to prevent unwanted pregnancies outside of physiological reproductive years.

Conclusion

The clinical application of OTC is undoubtedly feasible as a method of fertility preservation for medical indications and with more than 200 reported livebirths, it is no longer considered an experimental procedure. In the context of the societal trend of women delaying motherhood, the impact of ARFD is becoming increasingly prevalent, often resulting in involuntary childlessness or failure to meet reproductive aspirations. Women can now electively cryopreserve oocytes, however not without risks, including those associated with COS and being restricted to store a finite number of oocytes giving a reasonable

probability of achieving a livebirth based on the woman's age. As established from the evidence provided herein, EOTC could provide an alternative option to EOC, which overcomes some of these challenges, by facilitating spontaneous conception and not being curtailed by a limited number of oocytes for cryopreservation. However, given the novelty of this technology, further research, ethical reflection and legislative reform is required to help determine the suitability, cost-effectiveness, reproductive efficacy and sustainability of this procedure in the context of ARFD.

Authors' roles

L.S.K. drafted and revised the article for important intellectual content. S.S., N.G., H.O., T.B.-M., F.S., J.Y., M.-Y.T., J.N., J.B.N. and P.H. revised the article for important intellectual content. C.D.-G. provided substantial contribution to the analysis and interpretation of evidence and revised the manuscript critically for important intellectual content. B.P.J. conceived the idea of the manuscript, helped revise the article and provided final approval of the version to be published.

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Conflict of interest

The authors have no conflicts of interests to declare.

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