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

Lorraine S. Kasaven 1,2,3,*, Srdjan Saso1,2, Natalie Getreu4, Helen O’Neill5, Timothy Braceywell-Milnes6, Fevzi Shakir7, Joseph Yazbek1, Meen-Yau Thum6, James Nicopoulos6, Jara Ben Nagi8, Paul Hardiman7, Cesar Diaz-Garcia9,10, and Benjamin P. Jones 1,2

1West London Gynaecological Cancer Centre, Hammersmith Hospital, Imperial College NHS Trust, London, UK 2Department of Surgery and Cancer, Imperial College London, London, UK 3Cytara Perioperative and Ageing Group, Sir Michael Uren Hub, Imperial College London, London, UK 4Translational Ovarian Physiology and Pathophysiology, Institute for Women’s Health, University College London, London, UK 5Genome Editing and Reproductive Genetics Group, Institute for Women’s Health, University College London, London, UK 6Lister Fertility Clinic, The Lister Hospital, London, UK 7Royal Free London NHS Foundation Trust, London, UK 8Centre for Reproductive and Genetic Health, London, UK 9IVI London, IVIRMA Global, London, UK 10EGA Institute for Women’s Health, University College London, London, UK

*Correspondence address. Department of Surgery and Cancer, Imperial College London, Du Cane Road, London W12 0NN, UK. Tel: +44-07775679821; E-mail: lk226@doctors.org.uk

Submitted on February 12, 2022; resubmitted on May 29, 2022; editorial decision on June 9, 2022

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 in-
ability to meet reproductive aspirations. It is therefore unsurpris-
ing that as the age of first-time motherhood has increased, microsimula-
tion models used to estimate the rates of permanent involuntary child-
lessness 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%, re-
spectively) (Seenhof and De Jong, 2000; Te Velde et al., 2012). Adven-
tancements in artifical reproductive technology (ART) have pro-
vided women the opportunity to overcome such challenges by utilizing
oocyte donation for in vitro fertilisation (IVF) cycles. Although this en-
ables the experience of gestation, it denies the opportunity for biologi-
cally related offspring. Women wishing to preserve their fertility to
mitigate the impact of age-related fertility decline (ARFD) can now un-
dergo 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 medi-
cal 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 elec-
tive 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 associ-
ated 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 bar-
riers surrounding the hardening of the zona pellucida (Fabbri et al.,
1998). Technological advancements have since improved oocyte sur-
vival and reproductive outcomes (Smith et al., 2010), with similar im-
plantation, pregnancy, miscarriage and livebirth rates (LBRs) demonstra-
ted between fresh and cryopreserved oocytes (Cobo et al., 2010; Craw-
ford 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 educa-
tion 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 individual-
ized, comprehensive and realistic counselling regarding future out-
comes. 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 ex-
emplified by data showing oocyte thaw survival rates between 80%
and 90%, and fertilization rates following intracytoplasmic sperm injec-
tion (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 cryopre-
served oocytes (Ben-Rafael, 2018; Cobo et al., 2018; Gürün et al.,
2019; Kasaven et al., 2020). Consequently, successful LBRs of 17.5–
30.5% have been observed in such women (Gürün et al., 2019;
Kasaven et al., 2020), highlighting that EOC is a feasible method of fer-
tility preservation for ARFD. The chances of successful livebirth are de-
pendent 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 rec-
ommendations 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, demon-
strated 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 stimula-
tion is often required to achieve a favourable chance of livebirth.

The mean age at which women underwent EOC in one of the larg-
est 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 effi-
ciency per warmed oocyte, directly correlating to one successful live-
birth 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 (Lallemand 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) (Provost 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
transplanted into either the broad ligament, the remaining ovarian 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 reported edly between 27% and 37% (Bedaawy 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

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

| Advantages | Disadvantages |
|------------|--------------|
| Biological offspring is feasible | Offspring is not guaranteed |
| Invasive surgery and general anaesthesia is not required | More than one cycle of COS may be required to retrieve adequate oocyte numbers to improve chances of successful livebirth |
| Oocytes retain their reproductive potential from the age they were cryopreserved, with improved outcomes observed in younger women | Ovarian stimulation increases the risk (albeit minimal) of thrombotic events and OHSS |
| Similar outcomes between cryopreserved warmed oocytes and fresh IVF cycles | Undergoing ovarian stimulation is associated with short and long-term psychological effects in infertile couples |
| Procedure is cost-effective when cryopreservation is carried out at the optimal age | Poor outcomes including total number of oocytes retrieved, pregnancy and livebirth rates are associated in women undergoing the procedure >35 years old |
| Successful pregnancy, livebirth and perinatal outcomes have been reported | Oocytes may not end up being used, due to spontaneous conception, or through choice |
| Duration of cryopreserved oocytes does not affect the risk of aneuploidy or alter gene expression of the thawed oocytes | A finite number of oocytes are retrieved and cryopreserved |
| Procedure is associated with a low rate (%) of decision regret | |

**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

**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

**Advantages**

- 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
- 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.
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; Meirov 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 (Meirov, 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 (Herraz 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 when their reproductive potential has started to deteriorate, reimplantation of the cryopreserved ovarian tissue could be undertaken, thereby restoring or enhancing their 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 transcendent 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.

Funding
No funding was required for this paper.

Conflict of interest
The authors have no conflicts of interests to declare.

References
Alborzi S, Motazedian S, Parsanezhad ME. Chance of adhesion formation after laparoscopic salpingo-ovariolysis: is there a place for second-look laparoscopy? J Am Assoc Gynecol Laparosc 2003;10:172–176.
Andersen CY. Success and challenges in fertility preservation after ovarian tissue grafting. Lancet 2015;385:1947–1948.
Baldwin K. Motivations for social egg freezing. In: Egg Freezing, Fertility and Reproductive Choice (Emerald Studies in Reproduction, Culture and Society). Bingley: Emerald Publishing Limited, 2019, 69–85.
Baldwin K, Culley L, Hudson N, Mitchell H. Running out of time: exploring women’s motivations for social egg freezing. J Psychosom Obstet Gynaecol 2019;40:166–173.
Barcroft JF, Galazis N, Jones BP, Getreu N, Bracewell-Milnes T, Grewal KJ, Sorbi F, Yazbek J, Lathouras K, Smith JR et al. Fertility treatment and cancers—the eternal conundrum: a systematic review and meta-analysis. Hum Reprod 2021;36:1093–1107.
Beckmann MW, Dittrich R, Lotz L, Van Der Ven K, Van Der Ven HH, Liebenthal J, Korrêl M, Frambach T, Sutterlin M, Schwab R et al. Fertility protection: complications of surgery and removal and transplantation of ovarian tissue. Reprod Biomed Online 2018;36:188–196.

Beckmann MW, Lotz L, Toth B, Baston-Bust DM, Fehmt T, Frambach T, Germeyer A, Goekenian J, Haberlin F, Henes M et al. Concept paper on the technique of cryopreservation, removal and transplantation of ovarian tissue for fertility preservation. Geburtshilfe Frauenheilkd 2019;79:53–62.
Bedaiwy MA, El-Nashar SA, El Saman AM, Evers JL, Sandadi S, Desai N, Falcone T. Reproductive outcome after transplantation of ovarian tissue: a systematic review. Hum Reprod 2008;23:2709–2717.
Ben-Rafael Z. The dilemma of social oocyte freezing: usage rate is too low to make it cost-effective. Reprod Biomed Online 2018;37:443–448.
Bergh C, Pinborg A, Wenneholm U-B. Parental age and child outcomes. Fertil Steril 2019;111:1036–1046.
Birth Statistics. Review of the Registrar General on Births and Patterns of Family Building in England and Wales. London: Office for National Statistics, 2006 (13 May 2022, date last accessed).
Bjelland EK, Wilkosz P, Tanbo TG, Eskild A. Is unilateral oophorectomy associated with age at menopause? A population study (the HUNT2 Survey). Hum Reprod 2014;29:835–841.
Brod M, Verhaak C, Weibinga C, Gerris J, Hoomans E. Improving clinical understanding of the effect of ovarian stimulation on women’s lives. Reprod Biomed Online 2009;18:391–400.
Chen C. Pregnancy after human oocyte cryopreservation. Lancet 1986;327:884–886.
Cheong Y, Saran M, HounsloW JW, Reading IC. Are pelvic adhesions associated with pain, physical, emotional and functional characteristics of women presenting with chronic pelvic pain? A cluster analysis, BMC Womens Health 2018;18:11.
Chian R-C, Huang JY, Tan SL, Lucena E, Saa A, Rojas A, Castellón LAR, Amador MIG, Sarmiento JEM. Obstetric and perinatal outcome in 200 infants conceived from vitrified oocytes. Reprod Biomed Online 2008;16:608–610.
Christianson MS, Lukish DA, McCarter R, Pryor H, Lukish JR. Ovarian tissue cryopreservation in young females with cancer and its impact on ovarian follicle density. J Pediatr Surg 2021;56:2354–2359.
Chung EH, Lim SL, Myers E, Moss HA, Acharya KS. Oocyte cryopreservation versus ovarian tissue cryopreservation for adult female oncology patients: a cost-effectiveness study. J Assist Reprod Genet 2021;38:2435–2443.
Cil AP, Ban H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. Fertil Steril 2013;100:492–499.e3.
Cobo A, García-Velasco J, Domingo J, Pellicer A, Remohí J. Elective and onco-fertility preservation: factors related to IVF outcomes. Hum Reprod 2018;33:2222–2231.
Cobo A, García-Velasco JA, Coello A, Domingo J, Pellicer A, Remohí J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril 2016;105:755–764.e8.
Cobo A, García-Velasco JA, Domingo J, Remohí J, Pellicer A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil Steril 2013;99:1485–1495.
Cobo A, Garrido N, Pellicer A, Remohí J. Six years’ experience in ovum donation using vitrified oocytes: report of cumulative outcomes, impact of storage time, and development of a predictive
model for oocyte survival rate. *Fertil Steril* 2015;104:1426–1434.e8.

Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. *Hum Reprod* 2010;25:2239–2246.

Cobo A, Serra V, Garrido N, Olmo I, Pellicer A, Remohi J. Obstetric and perinatal outcome of babies born from vitrified oocytes. *Fertil Steril* 2014;102:1006–1015.e4.

Crawford S, Boulet SL, Kawwass JF, Jamieson DJ, Kissin DM. Cryopreserved oocyte versus fresh oocyte assisted reproductive technology cycles, United States, 2013. *Fertil Steril* 2017;107:110–118.

Delvigne A. Prediction and prevention of ovarian hyperstimulation syndrome. In: Rizk B, Gerris J (eds). *Complications and Outcomes of Assisted Reproduction*. Cambridge: Cambridge University Press, 2017, 124–140.

Devesa M, Tur R, Rodriguez I, Coroleu B, Martinez F, Polyzos NP. Cumulative live birth rates and number of oocytes retrieved in women of advanced age. A single centre analysis including 4500 women ≥38 years old. *Hum Reprod* 2018;33:2010–2017.

Devine K, Mumford SL, Goldman KN, Hodes-Wertz B, Druckenmiller S, Propst AM, Noyes N. Baby budgeting: oocyte cryopreservation in women delaying reproduction can reduce cost per live birth. *Fertil Steril* 2015;103:1446–1453.e2.

Diaz-Garcia C, Domingo J, Garcia-Velasco JA, Herraiz S, Mirabet V, Iniesta I, Cobo A, Remohi J, Pellicer A. Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study. *Fertil Steril* 2018;109:478–485.e2.

Dolmans MM, Donnez J, Camboni A, Demylle D, Amorim C, Van Langendonckt A, Pirard C. IVF outcome in patients with orthotopically transplanted ovarian tissue. *Hum Reprod* 2009;24:2778–2787.

Dolmans MM, Falcone T, Patrizio P. Importance of patient selection to analyze in vitro fertilization outcome with transplanted cryopreserved ovarian tissue. *Fertil Steril* 2020;114:279–280.

Dolmans MM, Jadoul P, Gilliaux S, Amorim CA, Luyckx V, Squifflet J, Donnez J, Van Langendonckt A. A review of 15 years of ovarian tissue bank activities. *J Assist Reprod Genet* 2013;30:305–314.

Dolmans MM, Von Wolff M, Poiriot C, Diaz-Garcia C, Cacciottola L, Boisnel N, Liebenthron J, Pellicer A, Donnez J, Andersen CY. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. *Fertil Steril* 2021;115:1102–1115.

Donnez J, Dolmans MM. Fertility preservation in women. *N Engl J Med* 2017;377:1657–1665.

Donnez J, Dolmans MM, Diaz C, Pellicer A. Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. *Fertil Steril* 2015;104:1097–1098.

Doye J, Richter KS, Lim J, Stillman RJ, Graham JR, Tucker MJ. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. *Fertil Steril* 2016;105:459–466.e2.

El Cury-Silva T, Nunes ME, Casalechi M, Comim FV, Rodrigues JK, Reis FM. Cryoprotectant agents for ovarian tissue vitrification: systematic review. *Cryobiology* 2021;103:7–14.

Eurostat. Women are having their first child at an older age. Eurostat 2020. [https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20200515-2 (13 May 2022, date last accessed).]

Fabbri R, Porcu E, Marsella T, Primavera M, Seracchili R, Ciotti P, Magrini O, Venturoli S, Flamigni C. Oocyte cryopreservation. *Hum Reprod* 1998;13:98–108.

Forman EJ, Li X, Ferry KM, Scott K, Treff NR, Scott RT Jr. Oocyte vitrification does not increase the risk of embryonic aneuploidy or diminish the implantation potential of blastocysts created after intracytoplasmic sperm injection: a novel, paired randomized controlled trial using DNA fingerprinting. *Fertil Steril* 2012;98:644–649.

Gavish Z, Peer G, Hadassa R, Yoram C, Meirow D. Follicle activation and ‘burn-out’ contribute to post-transplantation follicle loss in ovarian tissue grafts: the effect of graft thickness. *Hum Reprod* 2014;29:989–996.

Gluvovsky D, Riesta B, Sueldo C, Fiszbajn G, Repping S, Nodar F, Papier S, Ciapponi A; Cochrane Gynaecology and Fertility Group. Vitrification versus slow freezing for women undergoing oocyte cryopreservation. *Cochrane Database Syst Rev* 2014;9:CD010047.

Goldman KN, Kramer Y, Hodes-Wertz B, Noyes N, Mccaffrey C, Grifo JA. Long-term cryopreservation of human oocytes does not increase embryonic aneuploidy. *Fertil Steril* 2015;103:662–668.

Goldman R, Racovscky C, Farland L, Munné S, Ribustello L, Fox J. Predicting the likelihood of live birth for elective oocyte cryopreservation: a counselling tool for physicians and patients. *Hum Reprod* 2017;32:853–859.

Greenwood EA, Pasch LA, Hastie J, Cedars MI, Huddleston HG. To freeze or not to freeze: decision regret and satisfaction following elective oocyte cryopreservation. *Fertil Steril* 2018;109:1097–1104.e1.

Guo S, Yu Y, Zhang N, Cui Y, Zhai L, Li H, Zhang Y, Li F, Kan Y, Qin S. Higher level of plasma bioactive molecule sphenosine 1-phosphate in women is associated with estrogen. *Biochim Biophys Acta* 2014;1841:836–846.

Gurtin ZB, Morgan L, O’Rourke D, Wang J, Ahuja K. For whom the egg thaws: insights from an analysis of 10 years of frozen egg thaw data from two UK clinics, 2008-2017. *J Assist Reprod Genet* 2019;36:1069–1080.

Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet* 2001;2:280–291.

Henry L, Labied S, Fransolet M, Kirschvink N, Blacher S, Noel A, Foidart JM, Nisolle M, Munaut C. Isoform 165 of vascular endothelial growth factor in collagen matrix improves ovine cryopreserved ovarian tissue viability. *Reprod Biol Endocrinol* 2015;13:12.

Herraiz S, Monzo´S ,G o ´mez-Gime´nez B, Pellicer A, Dordov R, Peer G, Hadassa R, Yoram C, Meirow D. Follicle activation and ‘burn-out’ contribute to post-transplantation follicle loss in ovarian tissue grafts: the effect of graft thickness. *Hum Reprod* 2014;29:989–996.

Huisman D, Raymakers X, Hoomans E. Understanding the burden of ovarian stimulation: fertility expert and patient perceptions. *Reprod Biomed Online* 2009;19:5–10.

Jadoul P, Guilmain A, Squifflet J, Luyckx M, Votino R, Wyns C, Dolmans MM. Efficacy of ovarian tissue cryopreservation for...
fertility preservation: lessons learned from 545 cases. Hum Reprod 2017;32:1046–1054.

Jensen AK, Kristensen S, Macklon K, Jeppesen J, Fedder J, Ernst E, Andersen C. Outcomes of transplantsations of cryopreserved ovarian tissue to 41 women in Denmark. Hum Reprod 2015;30:2838–2845.

Jensen AK, Macklon KT, Fedder J, Ernst E, Humaidan P, Andersen CY. 86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children. J Assist Reprod Genet 2017a;34:325–336.

Jensen AK, Rechnitzer C, Macklon KT, Ifversen MRS, Birkebæk N, Clausen N, Sørensen K, Fedder J, Ernst E, Andersen CY. Cryopreservation of ovarian tissue for fertility preservation in a large cohort of young girls: focus on pubertal development. Hum Reprod 2017b;32:154–164.

Jones B, Rajamanoharan A, Kasaven L, Jalmbrant M, Green J, Mahmoud M, Oidia R, Saso S, Serhal P, Ben Naji J. The novel use of fertility quality of life (FertiQoL) treatment subscale to assess treatment acceptability in social egg freezing. Hum Fertil 2020b;1–9.

Jones BP, Kasaven L, L’Heveder A, Jalmbrant M, Green J, Makki M, Oidia R, Norris G, Bracewell Milnes T, Saso S et al. Perceptions, outcomes, and regret following social egg freezing in the UK: a cross-sectional survey. Acta Obstet Gynecol Scand 2020a;99:324–332.

Kano M, Sosulski AE, Zhang L, Saatcioglu HD, Wang D, Nagykery N, Sabatini ME, Gao G, Donahoe PK, Pépin D. AMH/MIS as a contraceptive that protects the ovarian reserve during chemotherapy. Proc Natl Acad Sci USA 2017;114:E1688–E1697.

Kasaven L, Jones B, Heath C, Oidia R, Norris G, Jalmbrant M, Serhal P, Ben-Nagi J. Analysis of ten years of social oocyte cryopreservation: a research article. Authorea Preprints 2020;https://doi.org/10.22541/au.160226405.50599698/v1.

Khandwala YS, Zhang CA, Lu Y, Eisenberg ML. The age of fathers in the USA is rising: an analysis of 168 867 480 births from 1972 to 2015. Hum Reprod 2017;32:2110–2116.

Kim SS, Yang HW, Kang HG, Lee HH, Lee HC, Ko DS, Gosden RG. Quantitative assessment of ischemic tissue damage in ovarian cortical tissue with or without antioxidant (ascorbic acid) treatment. Fertil Steril 2004;82:679–685.

Kol S, Humaidan P, GnRH agonist triggering: recent developments. Reprod Biomed Online 2013;26:226–230.

Kristensen SG, Andersen CY. Cryopreservation of ovarian tissue: opportunities beyond fertility preservation and a positive view into the future. Front Endocrinol 2018;9:347.

Kristensen SG, Liu Q, Mamsen L, Greve T, Pors S, Bjørn A, Ernst E, Macklon K, Andersen C. A simple method to quantify follicle survival in cryopreserved human ovarian tissue. Hum Reprod 2018;33:2276–2284.

Lallemant C, Vassard D, Nyboe Andersen A, Schmidt L, Macklon N. Medical and social egg freezing: internet-based survey of knowledge and attitudes among women in Denmark and the UK. Acta Obstet Gynecol Scand 2016;95:1402–1410.

Lass A. The fertility potential of women with a single ovary. Hum Reprod Update 1999;5:546–550.

Leonel ECR, Corral A, Risco R, Camboni A, Taboga SR, Kilbride P, Vazquez M, Morris J, Dolmans MM, Amorim CA. Stepped vitrification technique for human ovarian tissue cryopreservation. Sci Rep 2019;9:1–12.

Li F, Turan V, Lierman S, Cuveller C, De Sutter P, Oktay K. Sphingosine-1-phosphate prevents chemotherapy-induced human primordial follicle death. Hum Reprod 2014;29:107–113.

Lotz L, Dittrich R, Hoffmann I, Beckmann MW. Ovarian tissue transplantation: experience from Germany and worldwide efficacy. Clin Med Insights Reprod Health 2019;13:1179558119867357.

Lotz L, Maktabi A, Hoffmann I, Findelklee S, Beckmann MW, Dittrich R. Ovarian tissue cryopreservation and retransplantation—what do patients think about it? Reprod Biomed Online 2016;33:394–400.

Magnus MC, Wilcox AJ, Morken N-H, Weinberg CR, Häberle SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ 2019;364:i869.

Manavella D, Cacciottola L, Desmet C, Jordan B, Donnez J, Amorim C, Dolmans MM. Adipose tissue-derived stem cells in a fibrin implant enhance neovascularization in a peritoneal grafting site: a potential way to improve ovarian tissue transplantation. Hum Reprod 2018;33:270–279.

Martinez F. Update on fertility preservation from the Barcelona International Society for Fertility Preservation-ESHRE-ASRM 2015 expert meeting: indications, results and future perspectives. Hum Reprod 2017;32:1802–1811.

Masciangelo R, Hossay C, Donnez J, Dolmans M-M. Does the Akt pathway play a role in follicle activation after grafting of human ovarian tissue? Reprod Biomed Online 2019;39:196–198.

Meiorow D, Ra’anani H, Shapira M, Brenghausen M, Chaim SD, Aviel-Ronen S, Amarglio N, Schiff E, Orvieto R, Dor J. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril 2016;106:467–474.

Meiorow D. Fertility preservation in cancer patients using stored ovarian tissue: clinical aspects. Curr Opin Endocrinol Diabetes Obes 2008;15:536–547.

Mertes H. Does company-sponsored egg freezing promote or confine women’s reproductive autonomy? J Assist Reprod Genet 2015;32:1205–1209.

Morris G, Mavrelos D, Theodorou E, Campbell-Forde M, Cansfield D, Yasmin E, Sangster P, Saab W, Serhal P, Seshadri E. Effect of paternal age on outcomes in assisted reproductive technology cycles: systematic review and meta-analysis. F&S Rev 2020;1:16–34.

Naftalin J, Hoo W, Pateman K, Mavrelos D, Holland T, Jurkovic D. How common is amenorrhoea? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. Hum Reprod 2012;27:3432–3439.

Oktay KH, Marin L, Petrikovsky B, Terrani M, Babayev SN. Delaying ovarian tissue transplantation: is it prime time? Trends Mol Med 2021;27:753–761.

Olive DL, Pritts EA. Fibroids and reproduction. Semin Reprod Med 2010;28:218–227.

Pacheco F, Oktay K. Current success and efficiency of autologue ovarian tissue transplantation: a meta-analysis. Reprod Sci 2017;24:1111–1120.

Pickering SJ, Johnson MH. The influence of cooling on the organization of meiotic spindle of the mouse oocyte. Hum Reprod 1987;2:207–216.
Porcu E. Cycles of human oocyte cryopreservation and intracytoplasmic sperm injection: results of 112 cycles. *Fertil Steril* 1999; 72:52.

Provoost V, Tilleman K, D’Angelo A, De Sutter P, De Wert G, Nelen W, Pennings G, Shenfield F, Dondorp W. Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment. *Hum Reprod* 2014; 29:413–417.

Rosendahl M, Simonsen MK, Kjer JJ. The influence of unilateral oophorectomy on the age of menopause. *Climacteric* 2017; 20:540–544.

Rozen G, Avagliano S, Agresta F, Gook D, Polyakov A, Stern C. Salama M, Woodruff TK. New advances in ovarian autotransplantation to restore fertility in cancer patients. *Cancer Metastasis Rev* 2015; 34:807–822.

Saumet J, Petropanagos A, Buzzaglo K, Mcmahon E, Warraghi M, Mahutte N. No. 356-egg freezing for age-related fertility decline. *J Obstet Gynaecol Can* 2018; 40:356–368.

Shahsavari MH, Alves KA, Alves BG, de Lima LF, Vizcarra DAM, Berrocal DJD, Silva LM, da Silva YP, Zelinski MB, de Figueiredo JR et al. Impacts of different synthetic polymers on vitrification of ovarian tissue. *Cryobiology* 2020; 94:66–72.

Shapira M, Dolmans M-M, Silber S, Meirrow D. Evaluation of ovarian tissue transplantation: results from three clinical centers. *Fertil Steril* 2020; 114:388–397.

Sheshpuri S, Shahnazi M, Mobarak H, Ahmadian S, Bedate AM, Nariman-Saleh-Fam Z, Nouri M, Rahbarghazi R, Mahdipour M. Ovarian function and reproductive outcome after ovario-use for ovarian tissue transplantation: a systematic review. *J Transl Med* 2019; 17:396.

Silber S, Pineda J, Lenahan K, Derosa M, Melnick J. Fresh and cryopreserved ovary transplantation and resting follicle recruitment. *Reprod Biomed Online* 2015; 30:643–650.

Silber S. Ovarian tissue cryopreservation and transplantation: scientific implications. *J Assist Reprod Genet* 2016; 33:1595–1603.

Smith GD, Serafini PC, Fioravanti J, Yadid I, Coslovsky M, Hassun P, Alegretti JR, Motta EL. Prospective randomized comparison of human oocyte cryopreservation with slow-rate freezing or vitrification. *Fertil Steril* 2010; 94:2088–2095.

Soleimani R, Heytens E, Oktay K. Enhancement of neoangiogenesis and follicle survival by sphingosine-1-phosphate in human ovarian tissue xenotransplants. *PLoS One* 2011; 6:e19475.

Steenhof L, De Jong A. Afstel door uitstel:(Kinder) loos alarm? [From postponement to childlessness: False alarm?]. *Maandstatistiek van de Bevolking* 2000; 48:9–22.

Stigliani S, Moretti S, Anserini P, Casciano I, Venturini PL, Scaruffi P. Storage time does not modify the gene expression profile of cryopreserved human metaphase II oocytes. *Hum Reprod* 2015; 30:2519–2526.

Stoop D, Maes E, Polyzos NP, Verheyen G, Tournaye H, Nekkebroeck J. Does oocyte banking for anticipated gamete exhaustion influence future relational and reproductive choices? A follow-up of bankers and non-bankers. *Hum Reprod* 2015; 30:338–344.

Stoop D, Nekkebroeck J, Devroey P. A survey on the intentions and attitudes towards oocyte cryopreservation for non-medical reasons among women of reproductive age. *Hum Reprod* 2011; 26:655–661.

Takae S, Suzuki N. Current state and future possibilities of ovarian tissue transplantation. *Reprod Med Biol* 2019; 18:217–224.

Te Velde E, Habbema D, Leridon H, Eijkemans M. The effect of postponement of first motherhood on permanent involuntary childlessness and total fertility rate in six European countries since the 1970s. *Hum Reprod* 2012; 27:1179–1183.

Van der Ven H, Liebenthron J, Beckmann M, Toth B, Korell M, Krüssel J, Frambach T, Kupka M, Hohl MK, Winkler-Crepaz K et al.; FertiPROTEKT network. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and deliveries rate. *Hum Reprod* 2016; 31:2031–2041.

van Leeuwen FE, Klip H, Mooij TM, van de Swaluw AMG, Lambalk CB, Kortman M, Laven JSE, Jansen CAM, Helmerhorst FM, Cohlen BJ et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod* 2011; 26:3456–3465.

Van Loendersloot LL, Moolenaar LM, Mol BWJ, Repping S, Van Der Veen F, Goddijn M. Expanding reproductive lifespan: a cost-effectiveness study on oocyte freezing. *Hum Reprod* 2011; 26:3054–3060.

Vincent C, Pickering S, Johnson M. The hardening effect of dimethylsulphoxide on the mouse zona pellucida requires the presence of an oocyte and is associated with a reduction in the number of cortical granules present. *J Reprod Fertil* 1990; 89:253–259.

Vrijland W, Jeeekel J, Van Geldorp H, Swank D, Bonjer H. Abdominal adhesions: intestinal obstruction, pain, and infertility. *Surg Endosc* 2003; 17:1017–1022.

Vuković P, Kasum M, Orešković D, Ćehić E, Raguz J, Elezaj S, Beketić-Orešković I. Importance of ovarian tissue cryopreservation in fertility preservation and anti-aging treatment. *Gynecol Endocrinol* 2019; 35:919–923.

Zoll M, Mertes H, Gupta J. Corporate giants provide fertility benefits: have they got it wrong? *Eur J Obstet Gynecol Reprod Biol* 2015; 195: A1–A2.