Scientific Impact Paper (New)
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Scientific Impact Paper: Ovarian Tissue Cryopreservation for Non-Medical Reasons

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Plain Language Summary

Advancements in gender equality have led to many women postponing motherhood. As age advances, women may find it more difficult to conceive as both the quantity and quality of their eggs (oocytes) decrease. Consequently, women may opt to freeze their oocytes at a younger age for later use, to overcome the risks of age-related fertility decline, a process known as elective oocyte cryopreservation. Elective oocyte cryopreservation is considered a well-established method of fertility preservation, facilitating the storage of a number of oocytes that can later be fertilised during fertility treatment, when the woman is ready to start her family.

Ovarian tissue cryopreservation may be an alternative approach. It is a technique currently used to preserve fertility in women and girls who may become infertile following treatment for cancer and other medical conditions. Unlike oocyte cryopreservation, where individual mature oocytes are collected and frozen, ovarian tissue cryopreservation involves freezing a small piece of ovarian tissue. This tissue contains thousands of immature oocytes surrounded by supporting cells that help them grow and function. The tissue is surgically removed and frozen, then later thawed and reimplanted, allowing it to resume normal ovarian function and potentially release oocytes naturally. Ovarian tissue cryopreservation has advanced over the last several years, with 189 live births reported from the procedure since 2000. While the procedure is relatively rare, data now suggest that ovarian tissue

cryopreservation achieves comparable pregnancy and live birth rates compared to elective oocyte cryopreservation.

Unlike elective oocyte cryopreservation, ovarian tissue cryopreservation affords women the opportunity to conceive naturally and may allow for more than one live birth from a single piece of ovarian tissue. Consequently, this may make ovarian tissue cryopreservation more cost-effective than elective oocyte cryopreservation. Additionally, hormones produced by the reimplanted tissue could offer an alternative to existing hormone replacement therapies for menopause treatment, although ethical and legal discussion is needed due to the higher risk of obstetric complications in older women.

Consequently, given the limitations of elective oocyte cryopreservation discussed above, ovarian tissue cryopreservation has been suggested as an alternative method of fertility preservation for women who choose to delay motherhood for any reason, and not just for women whose fertility may be negatively impacted by other medical conditions or treatments. This paper discusses whether ovarian tissue cryopreservation can be used as an alternative to elective oocyte cryopreservation in this context. However, it is important to acknowledge that further scientific evidence through clinical trials is required before the procedure is implemented clinically.

1. Introduction

Women's reproductive aspirations have evolved over the past several decades, with many women choosing to delay motherhood (1, 2). In the UK, the average age of first-time motherhood increased from 26.7 in 1970 to 30.9 in 2023 (3, 4). While reasons for the trend of deferring childbearing vary, a recent cross-sectional survey found that the most common factor was the absence of a partner, with other reasons including waiting for economic security, education, or career progression (5).

Consequently, this trend increases the risk of age-related fertility decline, due to the decline in oocyte number and quality as age advances (6, 7).

Elective oocyte cryopreservation (EOC) is an established fertility preservation technique that gives women the opportunity to defer childbearing if they are not in a position to conceive (1, 8). In the UK, 1,759 oocyte cryopreservation cycles were conducted in women under 35 within 2022 alone, an increase of approximately 856% since 2012, with similar trends seen in the US, Australia, and New Zealand (9, 10). However, given the variable attrition rates during thawing, fertilisation, development to blastocyst, and ploidy status, subsequently compounded by multiple variables that impact implantation, pregnancy, and live birth rates; while it extends the window of reproductive opportunity, it cannot guarantee future offspring (11, 12). A large retrospective study (n=9,439) previously demonstrated that retrieval of 16-25 oocytes resulted in the highest live birth rate, albeit only slightly exceeding the rates demonstrated with collection of 6-15 oocytes (13). Consequently, given the average number of oocytes collected per EOC cycle is 9.3 (standard deviation [SD] ±0.5) (14), many women will require multiple stimulation cycles to bank an optimal number of oocytes (13, 15), which along with storage fees, costs associated with the subsequent necessary intra-cytoplasmic sperm injection (ICSI) and embryo culture, and potentially multiple frozen embryo transfer cycles, require significant financial outlay. If cryopreserved oocytes are exhausted prior to the achievement of reproductive aspirations, it is likely that the negative impact of age upon oocyte quality and number will render further autologous cycles unsuccessful (14).

Ovarian tissue cryopreservation (OTC) is an established method of fertility preservation in women at risk of iatrogenic premature ovarian insufficiency (POI) secondary to gonadotoxic chemotherapy or radiation (16). Since the first autologous OTC transplantation was reported in 2000, at least 189 live births have been reported following this procedure (17-19). Consequently, given the limitations

78 associated with EOC discussed above, OTC has been suggested as an alternative method of fertility
79 preservation for non-medical reasons (20). However, its applicability has yet to be comprehensively
80 evaluated. This scientific impact paper aims to explore the current evidence base for OTC, in the
81 context of a preventative measure for age-related fertility decline and propose areas for further
82 research.

83 This guidance is for healthcare professionals who care for women, non-binary and trans people. Within
84 this document we use the terms woman and women's health. However, it is important to acknowledge
85 that it is not only women for whom it is necessary to access women's health and reproductive services
86 in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and
87 obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the
88 needs of those individuals whose gender identity does not align with the sex they were assigned at
89 birth.

90

91 **2. Ovarian tissue cryopreservation**

92 OTC outcomes thus far have been evaluated in women undergoing the procedure for medical
93 indications, such as gonadotoxic chemotherapy, Turner syndrome, and severe recurrent endometriosis
94 (21, 22). In a recent meta-analysis by Khattak *et al.*, in which over 70% of participants underwent OTC
95 due to an underlying malignancy, OTC was associated with a pregnancy rate (PR) of 37% (95%
96 confidence interval [CI] 32-43%) and a live birth rate (LBR) of 28% (95%CI 24-34%) (18). Comparably,
97 in a recent meta-analysis, EOC achieved a similar LBR of 28.4% (SD ±12.3) (14). Likewise, a recent
98 systematic review and meta-analysis found that EOC and OTC had similar outcomes, with a PR of 34.9%
99 for EOC and 43.8% for OTC ($p>0.05$), and LBR of 25.8% and 32.3%, respectively ($p>0.05$) (23). As with
100 EOC, age at cryopreservation plays a significant role in determining OTC outcomes, with significantly
101 higher PR in those who undergo OTC aged 35 and under (odds ratio [OR] 0.35; 95%CI 0.13-0.92) (14,
102 18). However, comparisons between PR and LBR between the two methods should currently be

103 interpreted with caution, as OTC has yet to be evaluated in women without medical indications for the
104 procedure. Specifically, women undergoing OTC for medical indications may have altered reproductive
105 potential, owing to the nature of the disease or treatment modality necessitating fertility preservation
106 with OTC (24, 25).

107

108 Unlike EOC, which can only achieve live birth through assisted reproductive technologies (ART), OTC
109 affords women the opportunity to conceive naturally. In a recent meta-analysis by Erden *et al.* two-
110 thirds of deliveries were conceived naturally, with Khattak *et al.* similarly reporting 69% of live births
111 were achieved following natural conception (17, 18). Consequently, while OTC does not eliminate the
112 need for additional ART to achieve successful pregnancies in all women, most women undergoing OTC
113 for non-medical reasons are likely able to circumvent the associated financial expense of multiple IVF
114 cycles.

115

116 Perinatal outcomes following OTC also appear promising, although the absolute number of successful
117 pregnancies remains small (17). A recent systematic review and meta-analysis identified 170 newborns
118 from 122 women who had previously undergone OTC, 83% of whom had underlying malignancies
119 necessitating fertility preservation with OTC (17). Overall, perinatal outcomes for OTC were
120 comparable to global population statistics for rates of preterm birth, low birthweight infants, and
121 neonatal congenital abnormalities. However, the proportion of pregnancies complicated by pre-
122 eclampsia was higher at 9.4% following OTC, nearly double the background population rate of 5% (17),
123 although this elevated risk may be attributed to underlying comorbidities in oncology patients (17).
124 Consequently, pregnancy outcomes may be more favourable in women undergoing OTC for non-
125 medical reasons, although further research is required to confirm this.

126

127 According to a retrospective cohort study of women undergoing OTC for fertility preservation in the
128 context of malignancy (n=41), graft function persists for an average of 4-5 years (26), although some
129 case studies have reported continued graft function for up to 10 years (27). Consequently, as graft
130 function may persist for several years, recipients are afforded the opportunity to conceive multiple
131 offspring from a single graft without requiring repeat implantation procedures (28). Reflecting this,
132 Erden *et al.* reported that 27% (n=122) of women who conceived following OTC reported more than
133 one live birth (17). Moreover, a single ovarian cortex retrieval procedure can yield sufficient tissue for
134 up to three separate implantations, enabling additional procedures if needed to increase the
135 cumulative chance of achieving one or more live births (29, 30). A recent cost-effectiveness analysis
136 indicated that OTC is less expensive than oocyte cryopreservation ($10,032 vs $16,588), so it is
137 potentially a more cost-effective option for women trying to preserve their reproductive potential (31).

138

139 Cost is a key consideration for elective fertility procedures (32). While OTC is currently limited to
140 medical indications in the UK, parallels can be drawn from EOC to anticipate the associated financial
141 barriers of OTC as an elective fertility preservation procedure. EOC is currently predominantly offered
142 in the private sector, with 81% of oocyte cryopreservation cycles privately funded according to a recent
143 report by the UK Human Fertilisation and Embryology Authority (HFEA), highlighting the financial
144 barriers associated with elective fertility preservation, which would likely also extend to elective OTC
145 (33). Furthermore, in resource rich countries, like the UK, OTC is generally offered in specialised fertility
146 centres (34). Consequently, the specialist technical demands of laparoscopic tissue retrieval and
147 subsequent reimplantation, may create bottlenecks in service provision, resulting in a mismatch
148 between growing demand and available capacity, further exacerbating the associated cost of the
149 procedure. This indicates that alongside clinical efficacy and graft longevity, careful consideration of
150 cost, expertise, and geographic accessibility is essential when planning the implementation of elective
151 OTC services.

It is likely that many women who fulfil their reproductive aspirations before requiring graft implantation will not return to use their cryopreserved tissue. While with EOC, women can opt to discard or donate their oocytes, in OTC, where autologous use only is possible without immunosuppression to prevent graft rejection, it has been proposed that subsequent regrafting of ovarian tissue in postmenopausal women could be used for hormone replacement (35). The procedure might be appealing to women who wish to avoid exogenous hormones. However, there are no data on the efficacy or safety profile of this intervention (35, 36). Careful evaluation of this aspect of the intervention is therefore required prior to considering OTC as a method of treatment for menopausal symptoms. Furthermore, if the ovarian tissue were to be replaced in the pelvis in this context, it would also require effective non-hormonal contraception, such as bilateral tubal ligation or insertion of a copper intrauterine device performed at the time of implantation, to avoid unwanted pregnancy in a population at high-obstetric risk due to advanced maternal age (35, 37). While heterotopic replacement does not increase the risk of pregnancy, further data demonstrating sufficient and safe hormone production are required (38).

3. **Surgical technique**

Following routine laparoscopic entry, endoscopic scissors are used to create an incision at the fimbrial pole to dissect the ovarian cortex from the medulla (39, 40). The retrieved cortex should be 1.0-1.5mm thick, as primordial follicles exist approximately 0.8mm below the surface, before being cryopreserved as strips (39, 40). Monopolar and bipolar coagulation should be avoided during retrieval, as it can lead to a loss of primordial follicles (39).

When indicated, cryopreserved strips are thawed and reimplanted laparoscopically into the ovary, pelvic side wall, or both (22, 39, 41). Endoscopic scissors without coagulation can be used to prepare the transplantation site, where cortical strips can be affixed to the ovarian medulla or a peritoneal pocket, with sutures or fibrin glue (39, 41). While there is ongoing debate regarding the optimal

transplantation site and manner of fixation, successful live births have been reported from each method (39). Further evaluation is needed to establish standardised practice.

4. **Risks**

During cortex retrieval and graft implantation, the risk of laparoscopic-associated complications appears comparable to the surgical risk for benign gynaecological conditions (42). In the largest cohort study evaluating surgical outcomes in OTC (n=1302), the surgical complication rate was 0.2% during retrieval and 0.07% with implantation (43).

Removal of ovarian cortical tissue invariably leads to a reduction in ovarian reserve. Consequently, OTC may lead to iatrogenic POI, depending on pre-operative ovarian reserve and the proportion of ovarian tissue resected (16). However, existing data primarily reflect women undergoing OTC for medical indications, who are also exposed to gonadotoxic treatments, limiting the generalisability of POI risk to an elective population (16, 22). An alternate approach to estimating this risk is to consider outcomes following unilateral oophorectomy. In a large retrospective cohort study (n=23,580) the onset of menopause occurred one year earlier (44). Moreover, in a Danish cohort study, when unilateral oophorectomy occurred at ages 20, 30 and 45, menopause occurred at 44.7, 46.3 and 48.7 years-old, respectively (45). Consequently, these studies provide reassurance that substantial volumes of ovarian tissue can be resected without significantly affecting the timing of onset of menopause (44, 45). Nonetheless, further research is needed to quantify the risk of POI following OTC for non-medical indications, particularly in relation to baseline ovarian reserve and the volume of tissue cryopreserved.

Following tissue retrieval, women may attempt to conceive prior to reimplantation. Consequently, it is integral that the subsequent capacity to conceive is not impaired by OTC. Following resection and storage of ovarian tissue during OTC, women may be concerned that the associated reduction in

ovarian reserve, reflected by reduced serum anti-Müllerian hormone (AMH) levels, could hinder their chances of spontaneous conception (46, 47). Reassuringly, in women without an infertility diagnosis who are having regular periods, serum AMH does not predict PR or time to conception, providing a measure of reassurance for those considering OTC (48, 49). This finding aligns with outcomes observed following unilateral oophorectomy, where serum AMH levels decline significantly post-resection (46, 47). Despite this decline, a recent meta-analysis comparing fertility outcomes following unilateral oophorectomy and ovarian cystectomy for borderline ovarian tumours found PR was comparable between the two procedures (OR 0.92; 95%CI 0.60-1.42) (50). Moreover, in a retrospective cohort study, unilateral oophorectomy had a negligible impact on PR when compared to appendicectomy and cholecystectomy, reporting PRs of 48.5%, 41.0%, and 53.8%, respectively ($p>0.05$) (51). Consequently, unilateral oophorectomy appears to have a negligible impact on fertility, with the PR in women following unilateral oophorectomy comparable to those in women with both ovaries (50, 51). Therefore, while further long-term studies evaluating natural conception prior to reimplantation in OTC patients would be valuable, current evidence supports that OTC does not significantly reduce fecundity, providing reassurance for patients considering this procedure.

Following graft implantation patients are likely to begin trying to conceive, with a median time to pregnancy of 9 months reported (interquartile range 6-16 months) (17). However, as with EOC, the individual chance of achieving pregnancy and successful live birth following OTC remains uncertain, with LBRs in the region of 30% (18, 23). Outcomes are influenced by several factors such as age at OTC, maternal body mass index (BMI), smoking status, and alcohol consumption (52). Similarly, paternal age, BMI, smoking status, and alcohol consumption can affect semen quality, further affecting the likelihood of successful conception (53). Consequently, women considering OTC should be counselled in a manner similar to EOC, emphasising that while OTC may mitigate some aspects of age-related

fertility decline, it carries inherent limitations and does not guarantee successful reproductive outcomes.

5. Selection criteria

Individuals considering elective OTC would be assessed on a case-by-case basis, taking into consideration age and baseline ovarian reserve (16). Women with an AMH less than 0.5ng/mL (3.56pmol/L) would generally be deemed unsuitable for OTC, as the benefits of fertility preservation are uncertain in this patient cohort (16). Furthermore, women over 35 years of age are less suitable candidates, as PR from both natural conception and ART are significantly reduced among this age group compared to women aged 35 years and under (OR 0.35; 95%CI 0.13-0.92) (18, 54). A retrospective cohort study further illustrates this age-related decline, demonstrating a progressively reduced PR as age at OTC increases, from 41% in women under 30, to 33% at 30-34 years, 18% at 35-39 years, and 0% in women aged 40 years and over (55). These findings highlight that younger women with adequate ovarian reserve represent the group most likely to benefit from elective OTC, emphasising the importance of careful, individualised patient selection.

An individualised risk assessment of the following surgical risk factors is also required: BMI, previous abdominal or pelvic surgery, or severe endometriosis (56). In cases with significant adhesions, where the ovaries may lie deep within the Pouch of Douglas; EOC may be more appropriate, as the ovaries may be more accessible through the vagina.

6. Laboratory aspects

The European Society of Human Reproduction and Embryology (ESHRE) currently advises slow-freezing of ovarian cortex specimens as standard practice (16). This method involves controlled cooling of cortex tissue in a cryoprotectant solution (57). The addition of antioxidants, including N-acetyl-L-cysteine (NAC), may minimise the formation of reactive oxidative species following cryopreservation,

249 which can impair stromal cell function and contribute to follicular degeneration (58). Experimental
250 evidence for this was provided by Li *et al.*, who reported that the addition of 5mM of NAC during
251 freezing can reduce reactive oxygen species levels in thawed ovarian tissue by approximately 44%
252 (p=0.001) compared to controls (n=15), potentially enhancing graft longevity and pregnancy outcomes
253 following reimplantation (58).

254

255 Ensuring follicular and stromal cell viability is crucial for graft success in OTC patients (29, 59, 60).
256 Vitrification has been suggested as an alternative to slow-freezing techniques, in which cortex tissue is
257 stored in high concentrations of cryoprotectants and rapidly cryopreserved (61). However, there is a
258 limited number of babies born after vitrification (62). A recent meta-analysis demonstrated that
259 follicular viability was comparable between vitrification and slow-freezing, although vitrification
260 achieved a higher proportion of intact stromal cells (61). Given the importance of stromal cells in
261 primordial follicle health and activation, this could improve success rates in vitrified tissue (59, 60, 63).
262 Consequently, while vitrification shows promise, evaluation of PR/LBR between cryopreservation
263 methods is necessary to compare clinical success rates and reliably inform clinical guidance (16, 22).

264 **7. <u>Opinion</u>**

265 • Fertility preservation to avoid age-related infertility is becoming increasingly important due to
266 societal changes leading women to delay motherhood.
267 • Women wishing to preserve their fertility for non-medical reasons currently have the option
268 of elective oocyte freezing. However, there is interest in alternative methods.
269 • OTC is an increasingly common procedure in adult women undergoing gonadotoxic
270 chemotherapy, with over 189 live births reported since 2000, and it may have potential for
271 non-medical indications.
272 • Evidence in women undergoing fertility preservation for medical indications suggests OTC has
273 comparable success rates to EOC.

- OTC offers benefits such as the opportunity for natural conception and multiple conceptions from one graft.
- The risk of surgical complications from OTC matches that of laparoscopic surgery for benign gynaecological conditions.
- Robust prospective clinical trials evaluating OTC for non-medical reasons are needed to assess not only live birth rates and graft longevity, but also procedural safety, long-term endocrine function, psychosocial outcomes, and cost-effectiveness. Such data are essential to guide clinical implementation and support informed, evidence-based discussions with women considering elective fertility preservation.

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Conflicts of interest

Full disclosure of interests is available upon request.

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[Please note that the references have not been formatted yet]

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