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Outcomes of immature oocytes collected from ovarian tissue for cryopreservation in adult and prepubertal patients

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KEY MESSAGE

Oocyte in-vitro maturation and vitrification procedures after ex-vivo collection from ovarian tissue could be considered as an additional option for fertility preservation.

A B S T R A C T

The efficiency of oocyte in-vitro maturation (IVM) and vitrification procedures after ex-vivo collection from ovarian tissue were assessed according to patient age, number of retrieved oocytes and tissue transport conditions. The combined procedure was performed in 136 patients: 130 adults (mean 27.6 ± 5.6 years) and six prepubertal girls (mean 8.7 ± 2.3 years). A higher mean number of oocytes were collected in girls compared with adults (11.5 ± 8.0 versus 3.8 ± 4.2, respectively, $P < 0.001$) but the percentage of degenerated oocytes was significantly higher in girls (35.5% versus 17.1%, respectively, $P < 0.001$). IVM rates were significantly lower in prepubertal than postpubertal population (10.3% versus 28.1%, $P = 0.002$). In adults, a negative correlation was observed between number of retrieved oocytes and age ($P = 0.002$; $r = -0.271$); the correlation was positive between anti-Müllerian hormone (AMH) and number of collected oocytes ($P = 0.002$; $r = 0.264$). IVM rates were not correlated with AMH levels ($r = 0.06$) or age ($r = -0.033$). At present, nine oocytes and one embryo have been warmed in four patients and one biochemical pregnancy obtained. This suggests the combined procedure could be an additional option for fertility preservation.

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Introduction

New therapeutic strategies for cancer have led to great improvements in cure and survival rates in young cancer patients (Howlader et al., 2011). However, antineoplastic therapies may be associated with significant gonadotoxicity and young cancer survivors usually express a strong desire to preserve childbearing potential (Letourneau et al., 2012; Meirow et al., 2010; Scanlon et al., 2012). Therefore, fertility preservation is an emerging field that offers new hope for women and girls treated for cancer before or during their reproductive years. All oncological guidelines address this issue by recommending that young patients be informed regarding possible fertility risks associated with treatment and that they be referred to a fertility centre if required (Knight et al., 2015; Peccatori *et al.*, 2013). Different approaches for fertility preservation in women diagnosed with cancer have been reported (Chung *et al.*, 2013; Demeestere et al., 2013; Jeruss and Woodruff, 2009). Among them, ovarian tissue cryopreservation (OTC) has emerged as an alternative to the standard oocyte or embryo vitrification option. This experimental procedure has several advantages as it can be rapidly performed without ovarian stimulation, even in prepubertal girls or when chemotherapy has already started. It also offers the possibility of storing a large number of follicles within ovarian fragments that can be later transplanted to restore fertility (Meirow, 2008; Meirow et al., 2014; Rodriguez-Wallberg and Oktay, 2012). Since the first live birth after transplantation of cryopreserved ovarian tissue (Donnez et al., 2004), this technique has led to the birth of over 80 healthy babies and has an estimated success rate of 25–30% (Donnez and Dolmans, 2015; Jensen et al., 2015; Meirow et al., 2016; Van der Ven *et al.*, 2016).

Despite these encouraging results, some advanced cancers or disseminated diseases, such as leukaemia, are considered to pose a high risk of recurrence after ovarian tissue transplantation due to the potential presence of neoplastic cells within the tissue (Bastings et al., 2013). Moreover, progress must still be made to improve the success rate of the procedure. OTC preserves the primordial and primary follicles, while the antral follicles, which contain immature growing oocytes, do not survive the procedure (Gosden, 2002). During the process, the ovarian cortex is dissected and frozen, while the medulla containing all the growing follicles is usually discarded or stored to assess the presence of neoplastic cells. These immature oocytes represent an additional source of gametes after in-vitro maturation (IVM). The vitrified oocytes can be directly used later for IVF and embryo transfer without any risk of disease transmission.

At present, only a few studies have investigated the feasibility of a combined option that preserves both ovarian tissue and in-vitro matured oocytes (Abir et al., 2016; Fadini et al., 2012; Fasano et al., 2011; Revel et al., 2009). Three live births from in-vitro matured oocytes retrieved during ovarian tissue processing for cryopreservation were recently reported (Prasath et al., 2014; Segers et al., 2015; Uzelac et al., 2015) but the factors involved in the success of the procedure, including oocyte collection, IVM and live birth rates are still unknown.

Previous studies have shown that the combined procedure is feasible in paediatric patients, including prepubertal girls (Abir et al., 2016; Fasano et al., 2011; Revel et al., 2009). However, the viability, developmental competence and fertilization potential of oocytes from paediatric patients must be confirmed as no oocytes have been warmed for fertility restoration yet.

Proper handling of ovarian tissue that originates from an operating room not immediately adjacent to the embryology laboratory constitutes another challenge. Animal studies have confirmed that follicles are subject to acute ischaemia during transport, leading to adverse changes such as a decrease in glucose concentration or increase in apoptotic index in granulosa cells (Ferreira et al., 2001; Pedersen et al., 2004; Sakamoto et al., 2006; Wongsrikeao et al., 2005). To avoid these adverse effects, time of transport and processing before cryopreservation should be as short as possible. However, the effects of timing or temperature during tissue transport on IVM rates have not been carefully investigated. One strategy used to reduce ischaemic damage during ovary transport is to decrease the median transport temperature. Animal studies have suggested that lowering the storage temperature of ovaries during transport is required to maintain the developmental competence of oocytes (Matsushita et al., 2004). However, hardening of the zona pellucida, impaired microtubules and cytoskeleton and damaged cytoplasmic membranes have also been described in oocytes exposed to low temperatures (Bianchi et al., 2014; Lee et al., 2006; Mandelbaum et al., 2004). Only one study reported oocyte maturation rates according to transport time in humans and did not show any negative impact of longer transport times (Yin et al., 2016). Therefore, the impact of the timing of ovarian transport on the developmental competence of oocytes remains uncertain and needs further evaluation.

The present study assessed the efficiency of oocyte IVM and vitrification procedures after ex-vivo collection from ovarian tissue according to the age of the patients, the number of retrieved oocytes, and the timing of tissue transport.

Materials and methods

Ethical approval

The cryopreservation of ovarian tissue, including immature oocyte collection when feasible, was approved by the central Ethical Committee from Erasme Hospital on 16 September 2008 (reference number: P2004/122). All patients or parents were informed about the procedure and provided written informed consent.

Cryopreservation of ovarian tissue

Ovarian tissue biopsies or unilateral oophorectomy were carried out at Erasme Hospital or in one of the participating Belgian centres. Unilateral oophorectomy was usually proposed for prepubertal patients, women who were at major risk of premature ovarian failure, or in cases where it was surgically indicated (Imbert et al., 2014). Tissues were transported in Leibovitz L-15 medium (Life Technologies, Merelbeke, Belgium) at 4°C and processed in the IVF laboratory at between 15 min (on-site) and a maximum of 3 h from removal. Three groups were compared according to the duration of transport (15 min, less than 1 h and between 1 h and 3 h).

Ovarian tissue freezing procedures have been described elsewhere (Demeestere et al., 2003; Imbert et al., 2014). Briefly, the medulla was gently removed and the cortex was cut into small fragments (≈5 × 5 × 1–2 mm). Ovarian fragments were incubated in a cryoprotectant solution containing 1.5 M dimethyl sulfoxide (DMSO) and 0.1 M sucrose for 30 min and then frozen using a slow freezing protocol in a programmable freezing machine (Kryo 360, Planer, UK) before storage in liquid nitrogen.

Cumulus–oocyte–complex (COC) retrieval and IVM procedures have been described elsewhere (Fasano et al., 2011). All visible antral

Table 1 – Indication for ovarian tissue cryopreservation.

Indications	Total *n* (%)	Adults *n* (%)	Prepubertal *n* (%)
Breast cancer	62 (45.6)	62 (47.7)	–
Haematological diseases			
Lymphoma	24 (17.6)	24 (18.5)	–
Leukaemia	5 (3.7)	4 (3.1)	1 (16.7)
Haematological benign	8 (5.9)	4 (3.1)	4 (66.7)
Borderline tumours	3 (2.2)	3 (2.3)	–
Pelvic tumour (gynaecological carcinoma, urological carcinoma)	10 (7.4)	10 (7.7)	–
Solid tumour (carcinoma, sarcoma, medulo-blastoma)	16 (11.8)	15 (11.5)	1 (16.7)
Immunological disorders	8 (5.9)	8 (6.2)	–
Total	136	130	6

follicles were punctured before ovarian tissue dissection to collect COCs. After dissection, the discarded material was filtered through a cell strainer and transferred into a Petri dish to search for additional COCs. The maturation stage of oocytes with expanded surrounding cells was easily evaluated using the sliding technique while oocytes tightly enclosed in cumulus cells were considered to be immature. After staging, immature COCs were transferred into IVM Maturation Medium (Sage, IVM Kit media) supplemented with 75 mIU/ml FSH and 75 mIU/ml LH and incubated at 37°C in a 6% CO_2/20% O_2 humidified atmosphere. All COCs were denuded after 24 h and resting immature oocytes were subjected to an additional incubation of 24 h. The mature oocytes were directly vitrified or fertilized by ICSI and the embryos obtained vitrified. Standard protocols (Irvine, Vitrification Kit media) with aseptic devices (CryoBiosystem, VHS Kit) were applied for mature oocyte and embryo vitrification according to the manufacturer's instructions (Fasano et al., 2012, 2014).

Population

From November 2008 to August 2014, 162 patients between 1 and 36 years old underwent OTC procedures in Erasme Hospital to preserve their fertility. The inclusion criteria for the cryopreservation of ovarian tissue have been previously described (Demeestere et al., 2003).

Twenty-six patients were excluded from the analysis. Twenty-three of them were treated with chemotherapy before the OTC procedure (Dolmans et al., 2005). Most of these patients were diagnosed with haematological diseases (15/23). For these patients, ovarian tissue has been cryopreserved but no oocytes were collected for further IVM. The other three excluded patients were aged less than 5 years. As previously reported by others, no healthy oocytes were found in these very young girls (Revel et al., 2009). The combined oocyte vitrification procedure was performed for 136 patients, 130 postpubertal/adult patients (mean age 27.6 ± 5.6 years) and six prepubertal girls (mean age 8.7 ± 2.3 years). Indications for OTC were mostly breast cancer and haematological diseases in postpubertal/adult and prepubertal patients, respectively (**Table 1**). Ovarian biopsies were performed in 93.8% (122/130) of adults while 83.3% (5/6) of prepubertal patients underwent unilateral oophorectomy.

Statistics

Statistical analyses were performed using SPSS-21 software (IBM Corp., USA). Continuous variables were expressed as mean ± SD and compared using Student's *t*-test. Proportions were analysed using the chi-squared test. Linear correlations between two independent variables were analysed by calculation of the *r*-values (Pearson's moment-correlation coefficient); the significance (two-tailed probability values) of *r* coefficients were calculated on the basis of the correlation values. Values of $P < 0.05$ indicated statistical significance.

Results

Oocyte retrieval

A total of 705 oocytes were collected *ex vivo* during the OTC procedure. A total of 140 of them (19.9%) were degenerated while six oocytes were already at metaphase II (MII) stage and directly vitrified. Most of the MII oocytes were obtained after puncture of visible antral follicles (4/6) but two MII oocytes were collected in filtered material after dissection of the ovarian tissue. A higher mean number of oocytes were collected in prepubertal patients compared with adults (11.5 ± 8.0 versus 3.8 ± 4.2, respectively, $P < 0.001$) but the percentage of degenerated oocytes was also significantly higher in the younger population (35.5% versus 17.1%, $P < 0.001$) (**Figure 1**). For 31 patients out of 136 (22.8%), no oocytes were found during the combined procedure and for two patients only degenerated oocytes were collected (1.5%). All of them were postpubertal patients.

IVM rate

A total of 559 oocytes were subjected to IVM: 491 at germinal vesicle (GV) stage (87.8%) and 68 at metaphase I (MI) stage (12.2%). After IVM for 24–48 h, at least one mature oocyte or embryo was vitrified in 52.9% of the patients (72/136). The overall IVM rate, excluding MII oocytes retrieved during the procedure, was 25.9% (16.1% at 24 h and 9.8% at 48 h). The IVM rate obtained was significantly lower in the prepubertal population compared with the postpubertal population (10.3% versus 28.1%, $P = 0.002$) (**Tables 2 and 3**). The maturation process

Table 2 – Results obtained for adult patients according to the diseases.

Indication	Age (mean ± SD)	Number of ovarian fragments/patient (mean ± SD)	Number of oocytes retrieved /patients (mean ± SD)	MII oocytes obtained *n*/total (%)
Breast cancer ($n = 62$)	30.2 ± 3.7[a]	20.1 ± 7.8[a]	3.4 ± 4.3	56/209 (26.8)
Haematological diseases ($n = 32$)	23.4 ± 6.3[b]	23.9 ± 7.2[b]	4.2 ± 4.4	42/133 (31.6)
Others ($n = 36$)	26.6 ± 5.4[c]	18.4 ± 6.7[c]	4.3 ± 3.6	45/154 (29.2)
Total ($n = 130$)	27.6 ± 5.6	20.6 ± 7.6	3.8 ± 4.2	143/496 (28.8)

P-values (age): a vs b; a vs c < 0.001; b vs c < 0.05.
P-values (fragments): a vs b < 0.05; b vs c < 0.01.

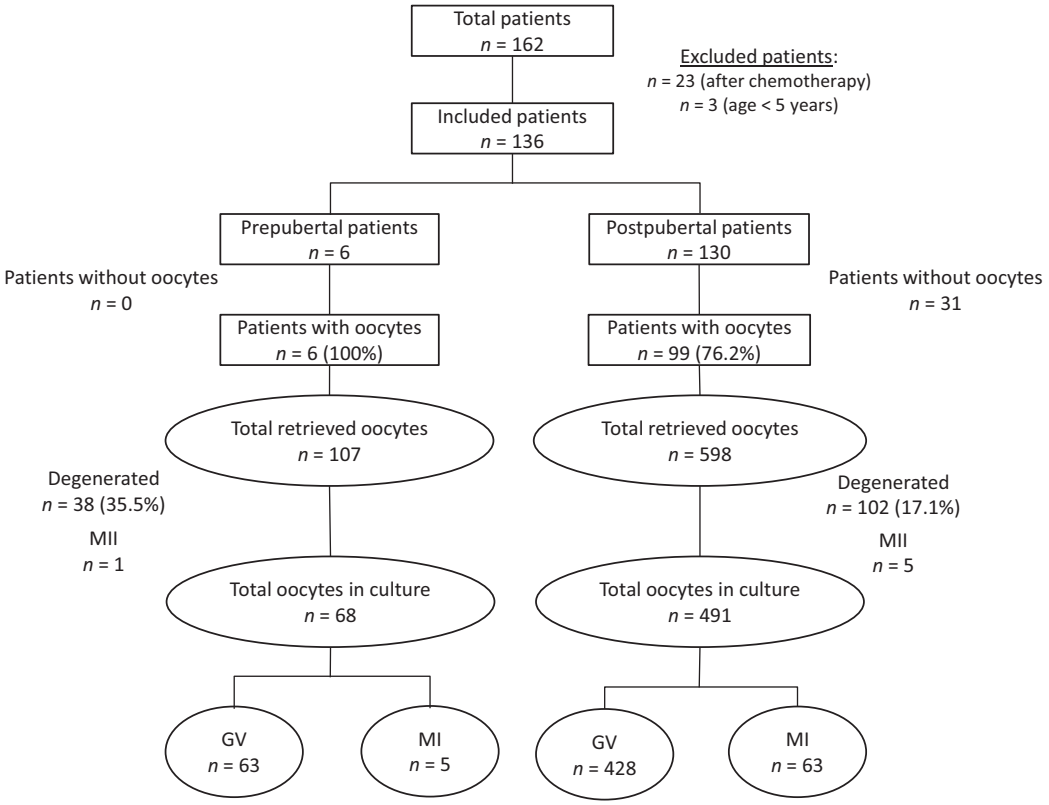


Figure 1 – Study population and oocytes retrieved (maturation stage details) in prepubertals and adults.

Table 3 – Results obtained for prepubertal patients.

Indication	Cases (*n*)	Age (years)	Fragments (*n*)	Oocytes retrieved (*n*)	MII oocytes obtained (*n*)
Leukaemia	1	8	36	14	2
Ewing sarcoma	1	13	17	2	0
Sickle cell anaemia	1	8	33	22	3
Sickle cell anaemia	1	6	25	19	1
Sickle cell anaemia	1	9	31	6	2
Sickle cell anaemia	1	8	21	6	0
Total (mean ± SD)	6	8.7 ± 2.3	27.2 ± 7.4	11.5 ± 8.0	8/69 (11.6%)

MII = metaphase II.

was also slower in prepubertal than in postpubertal patients with a majority of the oocytes matured after 48 h (**Figure 2**). In adults, a negative correlation was observed between the number of retrieved oocytes and age ($P = 0.002$; $r = -0.271$) while the correlation was positive between AMH and the number of collected oocytes ($P = 0.002$; $r = +0.264$). However, IVM rates were not correlated with AMH levels ($r = 0.06$) or age ($r = -0.033$).

Transport duration

The effects of transport time on maturation rates in postpubertal patients are reported in **Table 4**. IVM showed a trend towards higher rates with shorter transport times but the differences did not reach significance.

A total of 139 mature oocytes were vitrified in 72 patients and seven embryos (pronuclear stage embryos) were obtained after microinjection of 12 MII oocytes and vitrified in five patients. At present, four adults have asked to use their oocytes or embryos to try to conceive after cancer treatment. For three patients, nine oocytes vitrified in 2009/10 were warmed for fertility treatment. Only two oocytes survived (both vitrified after 48 h IVM) and were fertilized by ICSI, one low-quality three-cell embryo was obtained and transferred at day

Table 4 – In-vitro maturation rate according to transport time in adult patients.

Transport time (h)	Procedures (*n*)	Patient's age (mean ± SD)	Oocytes retrieved (mean ± SD)	In-vitro maturation rate (%)
15 min	39	26.0 ± 5.3	2.8 ± 2.9[a]	31.2
<1 h	72	28.2 ± 5.7	4.0 ± 4.3	29.1
1–3 h	19	28.2 ± 5.7	5.3 ± 5.3[b]	22.0

P-values a vs b = 0.02.

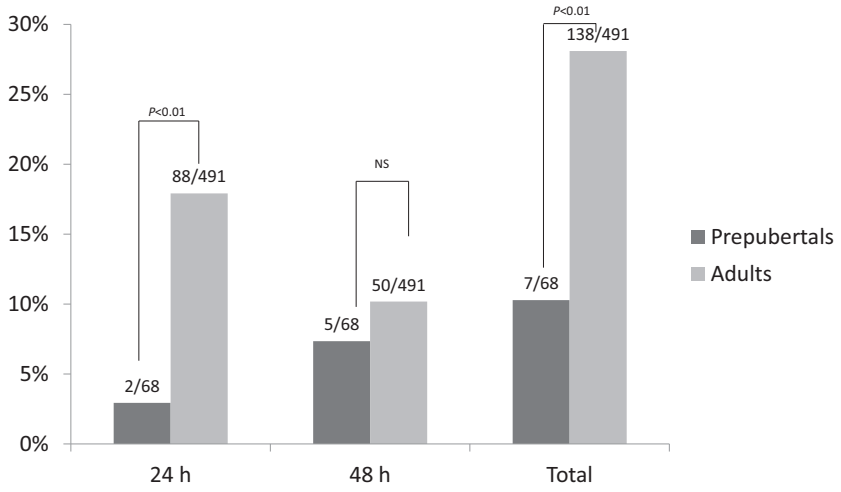


Figure 2 – In-vitro maturation rate in prepubertal patients and adults at 24 h and 48 h.

2 without pregnancy. For the fourth patient, a pronuclear stage embryo was warmed and a good quality four-cell embryo was transferred at day 2. Unfortunately, the patient had a biochemical pregnancy.

Discussion

The currently available options for preservation of fertility for cancer patients are to store gametes, embryos or gonadal tissue for later use. When OTC is offered, the combined ex-vivo retrieval of immature oocytes followed by IVM offers an additional chance to conceive, especially for patients who carry the potential risk of the presence of malignant cells in the ovary (Fadini et al., 2012; Fasano et al., 2011; Garcia-Velasco et al., 2013; Rosendahl et al., 2013).

While mature oocyte vitrification is now considered a standard procedure (Stoop et al., 2012), the efficiency of vitrification after IVM is less well established. However, previous studies have reported high cumulative clinical pregnancy rates using in-vitro matured oocytes in polycystic ovary syndrome (PCOS) patients (Junk and Yeap, 2012; Walls et al., 2012). Nevertheless, many aspects regarding IVM of ex-vivo retrieved oocytes need to be further addressed. COCs are exposed to suboptimal conditions during transport and dissection processes that may affect their competence and survival.

Researchers have recently reported cases of successful pregnancies and live births after the transfer of cryopreserved embryos obtained from oocytes collected *ex vivo* during OTC, matured *in vitro*, and fertilized by ICSI (Prasath et al., 2014; Segers et al., 2015; Uzelac et al., 2015). Segers et al. (2015) reported results on 34 patients who underwent a combination of OTC and IVM on ex-vivo collected oocytes. Most patients (32/34) underwent unilateral oophorectomy and the ovary was transported on ice to the IVF laboratory within 10 min (except for three patients). A mean of 14.7 ± 2.2 oocytes were collected per patient and the overall maturation rate reached 36.1 ± 4.3%. For one patient, 13 immature oocytes were retrieved, of which three embryos were cryopreserved. After a first unsuccessful attempt, the patient became pregnant using a second warmed embryo. Despite these encouraging results, the competence of these oocytes must be further investigated.

In our study, around 25% of the oocytes from adults were successfully in-vitro matured but only two out of nine oocytes survived the warming procedure. Almost all of them were obtained from ovarian biopsies. We expect that preservation of the whole ovary would provide the opportunity to retrieve more oocytes. Moreover, larger follicles can be punctured in intact ovaries to obtain potentially higher quality oocytes. The heterogeneity of the oocytes harvested *ex vivo* from cortex biopsies or whole ovaries may explain the lower IVM rates observed compared with classical COC protocols that nevertheless rarely exceed 50% (Sánchez et al., 2015). Finally, selection of the COCs in our study was less strict than in others as we included denuded oocytes and metaphase-I that may be of lower competence and quality.

However, we were able to obtain a biochemical pregnancy after transfer of a warmed embryo, suggesting that it might be feasible to obtain competent COCs from ovarian biopsies too.

Our results suggest that the procedure used here could be offered to prepubertal children but the degenerated oocyte rate in this population was higher than that of the adults. Moreover, maturation rates were also low, suggesting that these oocytes might be less competent than those obtained from the postpubertal/adult population. In agreement with other authors, we also suggest that patients less than 5 years of age are not suitable for ex-vivo oocyte collection and maturation (Abir et al., 2016; Revel et al., 2009). During the study period, we performed the combined procedure in three patients aged <5 years with no oocytes retrieved for two of them and no matured oocytes for the third one. As these three patients had ovarectomy, we expected to retrieve a high number of oocytes, but no healthy oocytes were obtained, confirming previous reports.

It has been shown that COCs can be obtained in patients aged >5 years old and the efficiency of the combined procedure has been evaluated in prepubertal patients. Revel et al. (2009) obtained a total of 179 oocytes in 17/19 patients (89%) aged 5–20 years. They found 7, 8 and 17 oocytes in the youngest patients aged 5, 8 and 10 years, respectively. The overall maturation rate was 45/133 oocytes (34%). In contrast with our results, the maturation rate was in the same range for these three youngest patients compared with the older patients. Another prospective study (Abir et al., 2016) was conducted in a cohort of 42 paediatric females aged 2–18 years who underwent combined OTC and IVM of oocytes collected during the procedure. Oocytes were obtained from 20 patients before chemotherapy and from 13 after chemotherapy. The youngest patients were aged 2 years and 3 years but no healthy oocytes were obtained. In this study, authors reported

a positive correlation between the number of vitrified oocytes and patient age ($P = 0.001$) but the percentage of cryopreserved oocytes over the total number of oocytes collected before chemotherapy ranged from 0% to 70% in patients less than 13 years old. In contrast, our data suggest that oocytes obtained after IVM in prepubertal children might be of lower quality than in the postpubertal population. However, the limited number of prepubertal patients in our study constituted a major limitation for the interpretation of the results and these data need to be confirmed in a larger cohort of patients. Nevertheless, they are supported by some experimental data. Recently, authors showed that prepubertal ovaries contained a high proportion of abnormal follicles (Anderson et al., 2014). Experimental results in animal models have confirmed that prepubertal follicles exhibited delays in meiotic progression and low developmental capacity (Leoni et al., 2015; Morton et al., 2008).

Most clinical protocols report that an oocyte IVM timing of between 24 h and 36 h provides the best balance between maturation rate and embryological outcome (Segers et al., 2015). In our study, IVM culture was extended up to 48 h for all the patients to rescue as many MII oocytes as possible, especially in prepubertal children, although the developmental capacity of 48 h in-vitro matured oocytes might be reduced (Ali et al., 2006; Chian et al., 2004; Sánchez et al., 2015). Overall, the discrepancy observed between studies raises questions about the future competence of vitrified oocytes in the prepubertal population but supports the potential benefit of this experimental procedure.

In our study, results showed that transport conditions did not significantly affect IVM rates despite a trend towards lower maturation rates with increasing transport times. Some authors have suggested that COC collection and maturation should only be attempted with oocytes from visible antral follicles and when the ovary is not subjected to a cooling period prior to recovery of immature oocytes (Wilken-Jensen et al., 2014). In the current study, the impact of transport duration was evaluated for a total of 130 procedures. The excised ovaries were transported to the laboratory either from the local hospital (15 min transport at 37°C) or from collaborating hospitals (1–3 h transport on ice). A higher maturation rate was obtained in immature oocytes collected from ovaries recovered at the local hospital compared with the other two groups, but the difference was not significant. Others have shown that transport up to 4–5 h on ice did not significantly affect oocyte maturation rates (Yin et al., 2016). Our results confirm that the transport of ovarian tissue should not be considered as a limitation for the combined procedure but it should be as short as possible to avoid potential impact on oocyte quality and survival.

This study on a large cohort of patients suggested that ex-vivo IVM should be considered as an additional fertility preservation option for women and children undergoing oophorectomy or ovarian tissue biopsy. Nonetheless, efficacy remains very low, especially for prepubertal patients. Future efforts should tailor and optimize not only cryopreservation, but also IVM protocols for use in either GV or MI oocytes, together with a comprehensive assessment of oocyte function and developmental competence to term.

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ARTICLE

In-vitro maturation of oocytes recovered during cryopreservation of pre-pubertal girls undergoing fertility preservation



BIOGRAPHY

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KEY MESSAGE

Pre-menarche girls, and in particularly those younger than 5 years of age undergoing in-vitro maturation during ovarian tissue freezing, may have a substantially decreased oocyte maturation rate compared with post-menarche girls. An alternative method for preserving fertility in those young patients should be considered.

ABSTRACT

Research question: In-vitro maturation (IVM) of oocytes recovered during ovarian tissue cryopreservation (OTC) is often practised, although it is still considered experimental. To date, only a few studies have examined the success of this maturation process in pre-menarche girls. The aim of this study was to examine the outcomes of IVM of oocytes recovered during OTC in pre-menarche patients scheduled for onco-therapy.

Design: A retrospective cohort study in a tertiary university-affiliated hospital. A total of 93 patients aged 0–25 years who underwent OTC as part of onco-fertility preservation between 2007 and 2019 were included in the study. Oocytes were recovered from the medium after OTC and matured over 48 h. Oocyte development and maturation rate were recorded and compared between different age groups.

Results: Patient's age was not correlated linearly with the total number of mature oocytes R = 0.2. The absolute maturation rate in post-menarche and pre-menarche patients differed significantly (38.0% versus 25.3%, respectively; $P > 0.001$), whereas the degeneration rate of the oocytes did not (39.8% versus 33.5%; $P = 0.167$). The pre-menarche group had significantly lower mean number of metaphase II oocytes compared with the post-menarche group (2.8 [±2.3] versus 5.6 [±4.6]; $P = 0.01$; 95% CI –4.62 to –0.46). Oocytes recovered from patients aged 1–5 years demonstrated low maturation rate.

Conclusions: Oocytes recovered from pre-menarche girls, and especially those younger than the age of 5 years who undergo fertility preservation, have a lower chance of reaching maturity in IVM compared with older women. This may indicate a need for alternative methods for preserving fertility in these young patients.

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KEYWORDS

Fertility preservation
In vitro maturation
Ovarian tissue Cryopreservation
Pre-menarche

INTRODUCTION

The increased survival rates of young women with cancer, together with advances in fertility preservation techniques, have led to a significant increase in the number of patients seeking fertility preservation (*Oktay, 2010*). Oocyte in-vitro maturation (IVM) is still considered an experimental alternative to ovarian stimulation for IVF (von Wolff et al., 2018).

The use of IVM in the paediatric-oncologic population is currently being practised, along with ovarian tissue cryopreservation (OTC) (*Revel et al., 2009*). In most patients, IVM does not supplant OTC, but it may serve as a complementary procedure. Several recent studies have reported IVM and vitrification procedures after ex-vivo collection from ovarian tissue to be a feasible approach (*Revel et al., 2009*; *Karavani et al., 2019*). For pre-pubescent girls who cannot undergo ovarian stimulation when only OTC is feasible, IVM oocytes provide an additional potential fertility reserve.

During the process of OTC, the ovarian cortex is dissected and then frozen, whereas the immature oocytes of the ovarian medulla, which may be used after undergoing IVM, represent a potential source of gametes, especially in certain cases of advanced cancer or disseminated diseases, such as leukaemia (*Dolmans et al., 2010*; *2014*). In the latter subset of patients, OTC may promote a high risk of recurrence of malignant disease upon tissue re-implantation owing to the potential presence of neoplastic cells within the tissue (*Bastings et al., 2013*). For those cases, successful IVM may provide a viable solution because vitrified oocytes can be directly used later for IVF, with a theoretical lower risk of reimplantation of malignant cells with a grafted tissue (*Donnez, 2018*).

Several studies have examined IVM rates in young oncologic populations (*Abir et al., 2016*; *Fasano et al., 2017*). *Karavani et al. (2019)* recently reported significantly lower immature oocyte yields and lower IVM rates in pre-menarche chemotherapy-naïve girls compared with older women. These findings were supported by others (*Fasano et al., 2017*), but firm conclusions were limited owing to small sample sizes. Conclusive data for supporting the efficacy of OTC and concurrent IVM in paediatric patients remain to be published. Although several births resulting from IVM oocytes have been reported in adults who underwent the procedure, no long-term follow-up results on paediatric patients who later achieved live births have been published (*Prasath et al., 2014*; *Segers et al., 2015*; *Uzelac et al., 2015*). The aim of this study was to assess the oocyte maturation rate in pre-menarchal girls undergoing OTC for fertility preservation. The outcomes were also compared with those of post-menarchal young women undergoing the same procedures in the same setting.

MATERIALS AND METHODS

Study design

This retrospective cohort study was conducted at a university-affiliated tertiary medical centre. The participants (n = 93) were recruited between December 2007 and June 2019, and included young patients who were referred to our fertility preservation services subsequent to malignancy diagnosis. They all underwent a laparoscopic oophorectomy for the purpose of ovarian tissue cryopreservation before chemotherapy, radiotherapy or other oncotherapy.

Settings

Patients' sociodemographic and clinical data were extracted from electronic medical records. The collected data included age, ethnicity, oncologic diagnosis, planned chemotherapy and radiation regimens, as well as age of menarche.

The laparoscopic oophorectomy took place at the paediatric surgery suits in the presence of a fertility specialist who transferred the excised ovary to the embryology laboratory in a cold phosphate buffered saline container.

Specifics of the IVM process of the oocytes were taken from the embryology laboratory charts. Information on the number of cryopreserved ovarian strips, the number of mature and immature oocytes retrieved during IVM and the total number of oocytes that had degenerated during maturation was recorded. The correlations between the IVM outcomes, the oocyte maturation rates, the total number of retrieved oocytes and the number of oocytes that matured to metaphase II (MII) were compared between the age groups of the study patients.

Tissue handling and cryopreservation

Ovarian tissue cryopreservation involved the separation of the ovarian cortex from the ovarian medulla, after which it was cut into 0.3 × 0.5-mm pieces. The pieces were transferred into a medium containing 1.5 M dimethyl sulfoxide and 20% serum. Between two to three pieces of ovarian cortex were placed in a 2-ml cryovial containing the cryoprotectant medium and processed by a slow-freeze with a Kryo 360 freezing machine. The tubes were then stored in liquid nitrogen. To preserve as many oocytes as possible, the remaining media containing the ovarian cortex were scanned for the presence of additional oocytes, and cumulus–oocyte complexes from the material were collected.

Oocyte maturation

All discovered oocytes (defined as day 0 oocytes) were transferred for up to 48 h of incubation in an oocyte maturation medium (Revel, 2009) (Sage In-Vitro Fertilization, Inc. Trumbull, CT, USA) supplemented with 0.075 IU/ml human menopausal gonadotrophin (Menopur) (Ferring Pharmaceuticals, Saint-Prex, Switzerland). After 24 h of incubation (defined as day 1 oocytes), the media were searched for mature MII oocytes, which were subsequently removed for freezing. The remaining oocytes were incubated for another 24 h and searched at 48-h intervals for additional MII oocytes (defined as day-2 oocytes). Mature metaphase II oocytes were vitrified by means of a Vitrification Kit (Sage In-Vitro Fertilization, Inc. Trumbull, CT, USA).

Quantitative variables

To establish the oocyte kinetics, several calculations were made: the total oocyte maturation rate was defined as (MII $_{[day\ 1]}$ + MII $_{[day\ 2]}$)/germinal vesicle [GV] $_{[day\ 0]}$ + metaphase I [MI] $_{[day\ 0]}$). The total oocyte degeneration rate was defined as (deg $_{[day\ 0]}$ + deg $_{[day\ 1]}$ + deg $_{[day\ 2]}$)/GV $_{[day\ 0]}$.

Statistical analysis

The Shapiro–Wilk test was used to assess cohort distribution; continuous data are presented as mean ± SD or median with interquartile ranges (IQR).

TABLE 1 PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Variable	*n* = 93
Age, years	15.4 ± 8.3[a]
Age at menarche, years	12.2 ± 1.2[a]
Post-menarche, *n* (%)	60 (64.5)
Pre-menarche, *n* (%)	33 (35.5)
Diagnosis, *n* (%)	
Sarcoma	43 (46.2)
Bone marrow and lymphatic system	21 (22.6)
Central nervous system tumours	11 (11.8)
Female reproductive system tumours	5 (5.4)
Other	13 (14.0)

[a] Mean ± SD.

The univariate analysis comprised the chi-squared test, Fisher's exact test for categorical variables and the Mann–Whitney U-test for non-normally distributed continuous variables. $P < 0.05$ was considered statistically significant. Pearson's correlation test was used to measure the statistical association between two continuous variables. A simple linear regression model was used to assess the potential relationship between the patient's age and IVM as well as the number of oocytes retrieved. SPSS 25 (IBM, St Louis, MO, USA) was used for statistical analysis.

Ethical approval

The Institutional Review Board (Helsinki) of the Tel Aviv Sourasky Medical Center approved this retrospective study (TLV-0216-20, approved 16.04.2020), and waived the need for written informed consent.

RESULTS

Demographics

During the study period, 93 patients between the ages of 0 and 25 years underwent laparoscopic oophorectomy for the purpose of ovarian preservation. Their sociodemographic features are presented in TABLE 1. The mean age of the entire group was 15.4 (± 8.3). A single ovary was successfully removed from each participant. The cohort comprised 33 pre-menarche patients and 60 post-menarche patients. The median age of pre-menarche girls was 7 years (IQR 5–11) and the median age of post-menarche women was 17 years (IQR 15–20).

TABLE 2.

The most common indications for carrying out OTC were diagnosis of sarcoma and other soft tissue tumours, comprising 46.2% of the study cohort (*n* = 43). Bone marrow and lymphatic system tumours were the second most frequent indication in this age group (*n* = 21 [22.6%]), followed by central nervous system tumours (*n* = 11 [11.8%]) and female reproductive tract tumours (*n* = 5 [5.4%]). None of the patients included in this study used their in-vitro matured oocytes for actual fertility purposes as of April 2020.

Oocytes collected with ovarian tissue cryopreservation

A total of 879 immature oocytes that were recovered from 64 of the 93 patients (68.8%) completed IVM and were subsequently been vitrified. The immature oocytes comprised 216 oocytes that were recovered from the pre-menarche patients and 663 oocytes from the post-menarche patients. The median number of oocytes recovered per patient included in the study was 11 (IQR 6–22). The likelihood of recovering more than one mature oocyte was 69.5% in the pre-menarche patients and 75.4% in the post-menarche patients ($P = 0.001$). Additionally, the likelihood of culturing at least one MII in the IVM culture was 43.1% among pre-menarche patients and 77% among post-menarche patients ($P = 0.03$). The data are not shown.

Oocyte maturation and degradation

The total oocyte maturation rate showed a weak linear correlation with age progression ($R^2 = 0.16$). The maturation rate of oocytes in post-menarche and pre-menarche patients differed significantly (31.0% versus 24.7%, respectively; $P > 0.001$). The total oocyte

TABLE 2 OVARIAN TISSUE CRYOPRESERVATION AND IN-VITRO MATURATION DATA

Variable	Post-menarche	Pre-menarche	
	n = 60	*n* = 33	P-Value
Total oocytes collected	663	216	
Size of pieces, mm^3 (IQR)	0.5 (0.3–1.0)		
Number of storage tubes (IQR)	20 (15–25)	18 (15–23)	
Oocytes (immature) per harvest (IQR)	10 (5–20.5)	6 (0–16)	(CI 95% −6.78 to 3.82) [c]
Mean number of MII oocytes[a] (day $_{1+2}$)	5.6 (±4.6)	2.8 (±2.3)	(CI 95% −4.62 to −0.46)[c] 0.01
Oocyte maturation rate, *n*, %	227/597 (38.0)	46/182 (25.3)	>0.001
Oocyte degradation rate, *n* (%)	189/565 (33.5)	69/173 (39.8)	0.14
Overall IVM rate[b]	23.3 (205)		
Overall degradation rate	29.4 (258)		

Data are presented as median (interquartile [IQR]) ranges and *n* (%).

[a] Excluding cases of non-retrieved oocytes.

[b] Excluding MII oocytes retrieved during the procedure.

[c] The difference between post- and pre-menarche.

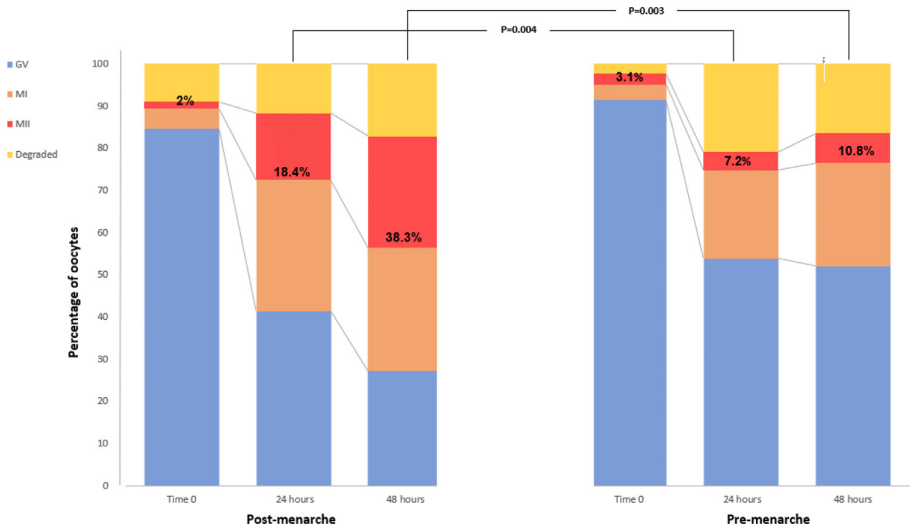


FIGURE 1 Oocyte maturation in 24-h intervals in pre-menarche versus post-menarche patients. GV, germinal vesicle; MI, metaphase I; MII, metaphase II.

degeneration rate, which was defined as (deg $_{[day\ 0]}$ + deg $_{(day\ 1)}$ + deg $_{(day\ 2)}$)/GV $_{[day\ 0]}$, showed almost no correlation with age progression (R^2 = 0.03). The absolute oocyte degeneration rate between post-menarche and pre-menarche patients did not differ significantly (39.8% versus 33.5%, respectively; *P* = 0.14).

An analysis of the post-menarche group was conducted using the coefficient correlation. This demonstrated a weak negative coefficient of (R = –0.012) between age and total number of MII. Similarly, a weak correlation was observed in post-menarche patients in oocyte degeneration rate through IVM (R = 0.13). This implies no differences in the results depending on the age and time since menarche.

The oocyte maturation course over 24-h intervals in both the post-menarche and pre-menarche patients is presented in FIGURE 1. The total number of MII oocytes in the post-menarche patients progressively increased with each 24-h interval. In comparison, the pre-menarche group showed only a modest change in the total number of mature MII oocytes with each 24-h interval. The pre-menarche group had a significantly lower number of total mature oocytes compared with the post-menarche patients at both the 24- and 48-h collection times (18.4% versus 7.2%, respectively; *P* = 0.004) and (38.3% versus 10.8%, respectively; *P* = 0.003). No statistically significant difference in MII proportion was observed at time zero (3.1% versus 2%; *P* = 0.67).

An additional sub-group analysis was conducted to assess the oocytes that were recovered from nine patients aged 1–5 years. A total of 58 oocytes were recovered, with a median of 4.5 (IQR 0–9) oocytes per patient. Of note, at the time of initial oocyte collection (oocytes $_{[day\ 0]}$), no MII oocytes were present in the medium and only two oocytes had matured during 48 h (MII $_{[day\ 1]}$ + MII $_{[day\ 2]}$) (data not shown).

DISCUSSION

The aim of this study was to investigate IVM of oocytes collected from the media during ovarian tissue processing for OTC carried out in young patients scheduled for oncotherapy. Another aim was to assess whether a correlation existed between patients' age and oocyte maturation rate. Our results suggest that, overall, post-menarche patients had a higher number of mature oocytes than pre-menarche patients. Additionally, the oocytes from the post-menarche group showed significantly more increased maturation rates to the MII stage after 24 and 48 h. These results demonstrate that IVM success, as defined and quantified as the collection of a larger number of mature oocytes after 48 h, was significantly greater in the post-menarche group compared with the pre-menarche group. Furthermore, the very young patients, i.e. aged 1–5 years, had the lowest maturation rate compared with all the other participants (3.4% reached MII).

Our results are in accordance with previous studies (*Segers et al., 2015*; *Karavani et al. 2019*), which demonstrated that oocytes recovered from a very young pre-menarche population had significantly lower IVM rates compared with post-menarche girls. In accordance with the data reported by *Revel et al. (2009)*, we found a significant difference in the mean number of oocytes collected per harvest between the examined age groups. We report a non-significant correlation between age and number of mature oocytes recovered for vitrification (R = 0.2), compared with *Abir et al. (2016)* who reported an age correlation, notably, however, before the onset of chemotherapy. Nonetheless, the population included in both studies were similar, which makes this comparison applicable. In contrast to our results, a recent study by *Fasano et al. (2011*; 2017) reported that a higher mean number of oocytes was collected in pre-pubertal patients compared with adult patients. Those investigators also reported an increased percentage of degenerate oocytes in pre-menarche girls, as well as a significant decrease in IVM rate in the same population. Our findings of significantly lower IVM rate in this age group were similar, in confirmation of their findings. We did not, however, find a significant increase in degeneration of oocytes.

We report a limited response in maturation of oocytes recovered from patients under the age of 5 years. Our findings are in accordance with another study (*Karavani et al., 2019*), which reported a lower total number of retrieved oocytes and lower maturation rates in this age group.

Extracorporeal oocyte maturation is apparently independent of the wide accepted notion suggesting 'an immature hypothalamic hypophyseal ovarian axis (*Rovner et al. 2018*)'. Hence, it is challenging to explain this substantial reduction in oocyte maturation in younger ages. These observations may be partially explained by the relatively high rate of aneuploidy often reported in a very young female population (*Hawkes, 2010*). The low natural fertility was attributed by *Gruhn et al. (2019)* to an increased rate of MI non-disjunction errors that they had observed in human oocytes recovered from young females. Further evidence is required to explain this significant difference.

The strengths of this study include a relatively large sample size of pre-menarche girls and detailed oocyte maturation status. The limitations of this study are mainly its retrospective design. None of the study patients has yet attempted to test the actual reproductive potential of their oocytes so that parameter still cannot be assessed.

In conclusion, oocytes recovered from pre-menarche patients followed by IVM demonstrated significantly lower rates of maturation throughout the days in the medium compared with the oocytes of post-menarche patients. Girls younger than 5 years of age undergoing fertility preservation characteristically show substantially decreased maturation rates, and this may point to the need for an alternative method for preserving fertility of very young patients facing onco-therapy.

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Twenty-first century oocyte cryopreservation—in vitro maturation of immature oocytes from ovarian tissue cryopreservation in cancer patients: A systematic review

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Abstract

Objectives: Our review aimed to consolidate the latest update on the application of in vitro maturation among immature oocyte harvest in combination with ovarian tissue cryopreservation known as ovarian tissue oocyte–in vitro maturation.

Methods: A thorough search for relevant studies was conducted via PubMed, Google Scholar, EMBASE, and clinical.gov databases up to December 2020. The primary outcome was the oocyte maturation rate, which measured the number of immature oocytes (geminal vesicle stage) that progressed to mature oocytes (meiosis II stage) following in vitro maturation. The secondary outcomes were the fertilization rate following intracytoplasmic sperm injection/in vitro fertilization of these oocytes for the embryo cryopreservation cohort. Our review included pre-pubertal girls and women with cancer who underwent ovarian tissue oocyte–in vitro maturation as fertility preservation.

Results: The primary search identified 207 studies. Twelve manuscripts were selected for inclusion in our review following duplication assessment, title and abstract screening, and full-text evaluation tailored to our inclusion criteria. All the population belonged to a cancer group and underwent concurrent ovarian tissue oocyte–in vitro maturation. A total of 5724 immature oocytes were obtained following ovarian tissue cryopreservation. Approximately 33.84% of the immature oocytes successfully matured via in vitro maturation, which were cryopreserved as oocytes or fertilized as embryos and subsequently stored for future use.

Conclusion: Our review proposed the potential application of ovarian tissue oocyte–in vitro maturation in increasing the number of mature oocytes. The acceptable improvement in oocyte maturation rate following in vitro maturation indicates that improving oocyte outcomes is an excellent cost-effective strategy for fertility preservation among women with cancer.

Keywords

cancer, fertility preservation, in vitro maturation, oocyte cryopreservation, ovarian tissue cryopreservation

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Introduction

Immature oocytes at the geminal vesicle (GV) stage are considered rested at the first meiotic prophase with a large nucleus. These oocytes are often discarded together with meiosis I (MI) oocytes as incomplete GV breakdown leads to maturation arrest without polar body production, which is not fertilizable. This oocyte stage is often discovered during control ovarian stimulation in standard in vitro fertilization (IVF) because of the asynchronized development of follicles, which leads to high cycle cancelation.[1–3] Most cases are observed among women with polycystic ovary syndrome (PCOS), as the standard stimulation is modified to reduce the risk of hyperstimulation syndrome, which resulted in a high number of immature oocytes.[4–6] In addition, the current implementation of fertility preservation (FP) among the cancer population leads to immature oocytes. To date, oocyte cryopreservation (OC) and ovarian tissue cryopreservation (OTC) are recommended for pre-pubertal girls and women before primary cancer treatment. Traditionally, OC is initiated during the follicular phase (FPh) following menstrual cycles to obtain a high number of meiosis II (MII) oocytes for cryopreservation. However, for FP purposes, most patients required immediate stimulation to avoid delay in initiating chemotherapy. Therefore, a random-start (RS) regime must be implemented in this case. Nevertheless, the RS stimulation often results in immature oocytes.[2,4,5,7–10] Previously, GV and MI oocytes were discarded, as they could not be cryopreserved. The finding leads to a less favorable outcome among the cancer population; thus, cycle repetition is proposed to overcome this problem. The implementation of in vitro maturation (IVM) in OC procedure does improve the overall number of mature oocytes and their ability to be cryopreserved. The IVM of oocytes was first reported in 1935 by Pincus and Enzmann.[11,12] They observed the spontaneous nature of the meiosis of rabbit ova removed from antral follicles. Four years later, Pincus and Saunders further consolidated the evidence using human oocytes.[11–13] Subsequently, IVM was developed, and it became an essential intervention in the veterinary field to breed rare and distinct species. Edward RG et al. had developed the IVM concept in maturating human oocytes since 1965, which led to the first IVM baby in 1991.[14,15] Since then, IVM had been implemented in improving infertility treatment and FP. At present, IVM is being used as a routine procedure in many centers with many live births reported worldwide.

On the contrary, OTC is recommended for pre-pubertal girls with cancer worldwide. It is also been a good option among women with cancer who have limited timing frame for oocyte stimulation prior to chemotherapy. In addition, this procedure is established following ovarian tissue transplantation. To date, at least 60 live births are reported worldwide. Similarly, many immature oocytes are harvested during ovarian cortical dissection for tissue cryopreservation. Previously, these oocytes are discarded, and only tissue cryopreservation is performed. Conversely, the debate regarding the risk of minimal residual disease (MRD) following ovarian tissue transplantation, particularly in hematological cancer, initiates the urge of utilizing these immature oocytes obtained during OTC as a safe gamete source for future fertility use, as the risk of MRD is eliminated.

Therefore, based on the successful outcome in OC following IVM, the idea of combining IVM following OTO (ovarian tissue oocyte–in vitro maturation)[16] has received considerable attention to improve the outcome of FP.[2,8,17] In this procedure, the immature oocytes collected during the OTC can mature via IVM and subsequently cryopreserved together with ovarian tissue. This method allows double utilization of FP methods, namely, OC and OTC, to improve FP among pre-pubertal girls and women. At present, the implementation of OTO-IVM has been widely proposed. Despite emerging evidence regarding OTO-IVM, this method remains unclear, as it is still considered at the initial stage of implementation.

Hence, our review aimed to summarize the current knowledge on OTO-IVM and consolidate the evidence of such use. In this review, we evaluated the number of immature oocytes yielded following OTC and the oocyte maturation rate (OMR) following IVM use and fertilization rates among post-IVM oocytes used in intracytoplasmic sperm injection (ICSI)/IVF. This finding can be used to strengthen the current evidence in establishing the recommendation of OTO-IVM in FP settings.

Methods

Protocol registration and search strategy

Our manuscript was formulated on the basis of the recommendation by Preferred Reporting Items for Systemic Reviews and was registered under Prospective International Register of Systematic Reviews (register no. CRD42021253406).[18,19] The ethical approval for systematic review (SR) is not required. Relevant studies within 20 years (2000–2020) were thoroughly searched in October 2021. The keywords used in PubMed search were as follows: "in vitro oocyte maturation techniques" [MeSH Terms] OR "vitro" [All Fields] AND "oocyte" [All Fields] AND "maturation" [All Fields] AND "techniques" [All Fields] OR "in vitro oocyte maturation techniques" [All Fields] OR "in vitro oocyte maturation techniques" [MeSH Terms] OR "vitro" [All Fields] AND "oocyte" [All Fields] AND "maturation" [All Fields] AND "techniques" [All Fields] OR "in vitro oocyte maturation techniques" [All Fields] OR "oocyte" [All Fields] AND "vitro" [All Fields] AND "maturation" [All Fields]. For Google Scholar search, "in vitro maturation ovarian tissue" OR "in vitro

maturation ovarian tissue cryopreservation" was used as keywords. Subsequently, the keywords "IVM," "OTC," "immature oocytes," "ovarian tissue cryopreservation," "oocyte cryopreservation," and "in vitro maturation" were used for clinical.gov database search, and the keywords "ovarian tissue cryopreservation" and "in vitro maturation" were used for EMBASE database search. The references of the selected studies were also collected, and all studies were subjected to duplication evaluation using EndNote® version 20.0.1. We also improved our search for potential manuscripts by performing a manual search using the reference lists obtained from related articles.

Study selection, data extraction, and risk of bias assessment

Following the primary search, the titles and abstract of manuscripts were initially evaluated by three authors (A.M.F, Y.S., and S.T.). The inclusion criteria were as follows: English language, original articles from January 2000 to December 2020, IVM as intervention following OTC in women with cancer for FP, and OMR as the primary outcome. The selected articles were subjected to full-text screening. Review articles, case reports, studies that describe OTC procedure without IVM, and non-English manuscripts were excluded. Subsequently, all the manuscripts were reviewed independently. The included manuscripts described the type of study, participant cohort, and number of immature and successfully matured oocytes following IVM and used OMR as an outcome. Any conflicts among the authors were resolved through discussion and another opinion by the fourth author (N.S). The National Institutes of Health (NIH) tool for observational studies was used for quality assessment.[20] The evaluation was further conducted by rating each of the 14 variables as 1 for "yes" and 0 for "no" or "non-applicable (NA)." The studies were further categorized as poor (0–5), fair (6–9), or good (10–14) based on the total score. All data from the included studies were tabulated accordingly (Table 1). All the included studies in our review obtained a minimum fair score (Table 2). The data were extracted on the basis of author's last name, year of publication, number, type of cohort, age of participants, mean oocytes retrieved from each patient, number of immature and mature oocytes following IVM, the ability of oocytes to be cryopreserved, and the mean OMR of each study as the primary outcome. In addition, the fertilization rate, pregnancy rate, biochemical pregnancy, clinical pregnancy, and live birth were recorded as the secondary outcomes if available.

Results

About 207 studies were discovered in the primary search (Figure 1), and 48 articles were discarded after duplication evaluation via EndNote®. The titles and abstracts of the remaining 159 articles were screened independently in accordance with the inclusion criteria. Subsequently, 128 articles were excluded, and 31 articles proceeded with the full-text evaluation. A total of 19 articles were further excluded; nine were not suitable, and 10 had no full text available (poster presentation or proceedings). Finally, 12 relevant articles were compiled for this review. The selected articles were critically evaluated for quality and bias as described in the Methodology (Supplementation 1).

Demographic profile of included studies

Based on the included studies, 590 patients with cancer received concurrent OTC as part of FP treatment.[21–32] At least 7.12% (n = 42) of patients were pre-pubertal (less than 12 years old), whereas 92.88% (n = 548) of patients were post-pubertal. The mean age in the pre- and post-pubertal groups was 7.04 and 25.15 years, and the youngest patient was 3.66 years old. In our review, almost all OTCs were performed via unilateral oophorectomy or wedge resection of the ovarian cortex, except for one patient who underwent bilateral oophorectomy for risk reduction surgery for BRCA1 mutation.[30] In addition, in one study, OTC was performed after oocyte retrieval following stimulated cycles (ST).[28] Otherwise, all other OTCs were performed in non-stimulated (NS) ovaries. All included studies utilized single-cycle IVM, except for one study that performed two cycles of IVM (one was conducted during the FPh, and the second was concurrent with the IVM procedure).[28] The summaries of the included studies are tabulated in Table 1.

Primary outcome

A total of 5724 oocytes were retrieved in includes studies with concurrent OTC. The mean oocyte retrieval was 11.27 oocytes for each patient. Following IVM, 1937 oocytes reached MII with OMR of 33.84%. Afterward, 1169 oocytes were successfully cryopreserved (Table 2).

Secondary outcome

About 118 embryos were obtained following IVF/ICSI with 64.53% of mean fertilization rate in post-IVM oocytes. All embryos were cryopreserved. In addition, no record of pregnancy rates and biochemical, clinical, and live birth was found, as all of our studies included utilized FP (Table 3).

Discussion

This review found that OTO-IVM could improve FP treatment outcome among cancer population. Following IVM, the OMR affects the number of mature oocytes that can be either directly cryopreserved or utilized via ICSI/IVF for

Table 1. Summary of the results from 21 included articles identified in a systematic review of the literature.

Number	Author, year	Study design	Sample size	Mean age	Number of IVM oocytes	Number of mature oocytes after IVM	Number of oocytes/embryo's cryopreserved or number of Embryo's yield after IVM	Intervention	Outcome
1	Ingrid et al.[30]	Retrospective	77 Pre-pubertal—9 Adults—68	24.5 ± 8.5	1220	494	448—OC 26—EC	Unilateral oophorectomy and OTC-IVM	Mean oocytes retrieved: 15.84 Maturation rates—pre-pubertal: 22% Maturation rates—post-pubertal: 42% Fertilization rates: 76.9% Mean embryo cryopreserved: 2.0 ± 2.0 Mean oocytes cryopreservation: 6.7 ± 6.3
2	Gilad et al.[27]	Retrospective	84 33 pre-menarche 51 post-menarche	Pre-menarche 0–4 years old: 3.66 Pre-menarche 5–10 years old: 8.10 Post-menarche 11 years old	736	179	NS	Unilateral oophorectomy and OTC-IVM	Mean oocytes retrieved—pre-pubertal: 8.07 ± 6.83 Group 0–4 years old: 4.69 ± 5.22 Group 5–10 years old:10.31 ± 7.02 Maturation rates—pre-pubertal: 15.5% Group 0–4 years old: 4.9% Group 5–10 years old: 18.2% Mean oocytes retrieved—post-pubertal: 10.77 ± 8.5 Maturation rates—post-pubertal: 28.2%
3	Ingrid et al.[31]	Prospective	34	6.6 years old pre-pubertal 29.1 years old post-pubertal	505	182	130—OC 20—EC	OTC-IVM 32—unilateral oophorectomy, 1—bilateral oophorectomy, 1—bilateral ovarian biopsy	Mean oocytes retrieved: 14.7 ± 2.2 Maturation rates—pre-pubertal: 18 ± 7% Maturation rates—post-pubertal: 40 ± 5% Fertilization rates: 65 ± 11% Embryo cryopreserved: 20 Oocytes cryopreservation: 130
4	Jens et al.[10]	Prospective	12	27.3 ± 4.8	37	14	8—OC	Unilateral ovarian resection—IVM	Mean oocytes retrieved: 3.1 ± 2.1 Oocytes maturation rates: 38.9%
5	Dmitry et al.[29]	Prospective	25	28 years old	895	274	N.S	Unilateral oophorectomy and OTC-IVM	Mean oocytes retrieved: 36 ± 5 Oocytes maturation rates: 31%
6	Jack et al.[17]	Retrospective	4	28	11	8	8—OC	OTC-IVM 1—unilateral oophorectomy, 3—ovarian wedge resection	Mean oocytes retrieved: 2.75 Oocytes maturation rates: 79.25% Oocytes cryopreservation: 100%
7	Nathalie et al.[32]	Prospective	17	32.6 ± 5.0	263	157	157—OC	Non-stimulated cycle and OTC + with double IVM cycles	Mean oocytes retrieved: 7.75 Oocytes maturation rates: 57.15% Oocytes cryopreservation: 50%
8	Ettie et al.[28]	Retrospective	18	23.7	286	170	EC—67 OC—67	Simulated IVF + ovarian tissue resection—OTC	Mean oocytes retrieved: 15.2 Oocytes maturation rates: 53.5% Fertilization rates: 66.25%
9	Giovanna et al.[23]	Prospective	57	23.1	225	70	EC—5 OC—52	Unilateral oophorectomy and ovarian wedge resection—OTC + IVM	Mean oocytes retrieved: 4 Oocytes maturation rates: 31% Fertilization rates: 50%
10	Maria et al.[21]	Prospective	33	31.5 ± 5.2	108	39	OC—21	Ovarian tissue resection—OTC + IVM	Mean oocytes retrieved: 3.3 ± 0.7 Oocytes maturation rates: 36.1%
11	Giovanna et al.[22]	Prospective	136	Adults 27.6 ± 5.6 Pre-pubertal 8.7 ± 2.3	559	145	OC—145	Unilateral oophorectomy and ovarian wedge resection—OTC + IVM	Mean oocytes retrieved adults: 4.6 Mean oocytes retrieved pre-pubertal: 17.8 Oocytes maturation rates adults: 28.8% Oocytes maturation rates pre-pubertal: 11.6%
12	Yuval et al.[24]	Retrospective	93	15.4 ± 8.3	879	205	OC—133	Ovarian tissue resection—OTC + IVM	Mean oocytes retrieved adults: 10 Mean oocytes retrieved pre-pubertal: 16 Oocytes maturation rates overall: 23.3% Oocytes maturation rates adults: 38% Oocytes maturation rates pre-pubertal: 25.3%

IVM: in vitro maturation; OC: oocyte cryopreservation; NS: non-stimulated; OTC: ovarian tissue cryopreservation; IVF: in vitro fertilization.

Table 2. Mean number of oocytes retrieved.

Number	Author, year	Number of immature oocytes	Mean oocytes retrieved	Number of mature oocytes after IVM	Number of oocytes cryopreserved after IVM	Oocytes maturation rates (OMRs)
1	Ingrid et al.[30]	1220	15.84	494	448	40.49%
2	Gilad et al.[27]	736	8.46	179	*Not stated*	24.3%
3	Ingrid et al.[31]	505	14.7 ± 2.2	182	130	36.03%
4	Jens et al.[10]	37	3.1 ± 2.1	14	8	38.9%
5	Dmitry et al.[29]	895	36 ± 5	274	*Not stated*	31%
6	Jack et al.[17]	11	2.75	8	8	79.25%
7	Nathalie et al.[32]	263	7.75	157	157	57.15%
8	Ettie et al.[28]	286	15.2	170	67	53.5%
9	Giovanna et al.[23]	225	4	70	52	31%
10	Maria et al.[21]	108	3.3 ± 0.7	39	21	36.1%
11	Giovanna et al.[22]	559	11.2	145	145	25.94%
12	Yuval et al.[24]	879	13	205	133	23.32%
Total		5724	11.27	1937	1169	33.84%

IVM: in vitro maturation.

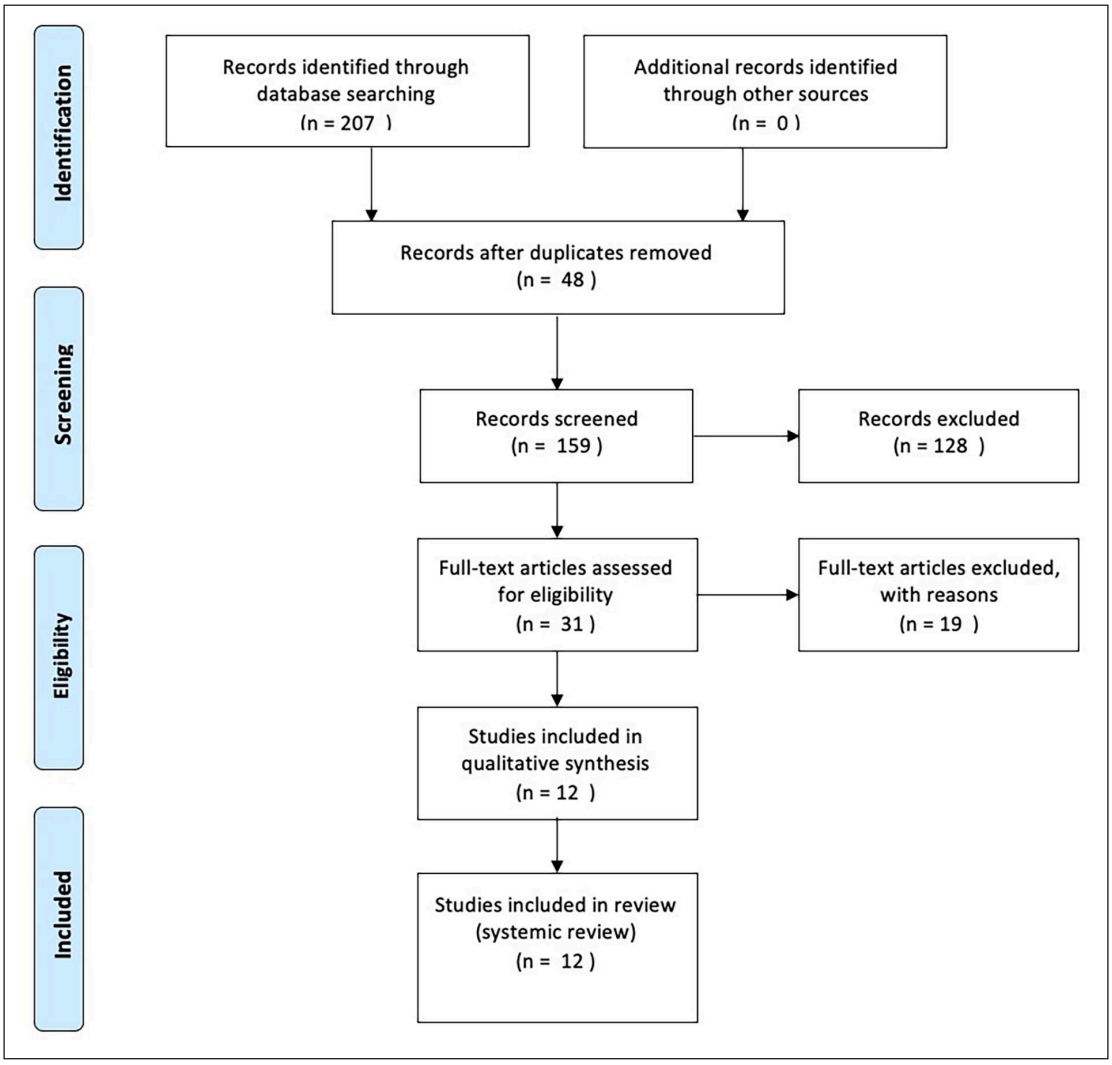


Figure 1. PRISMA flow chart of searching strategy.[20]

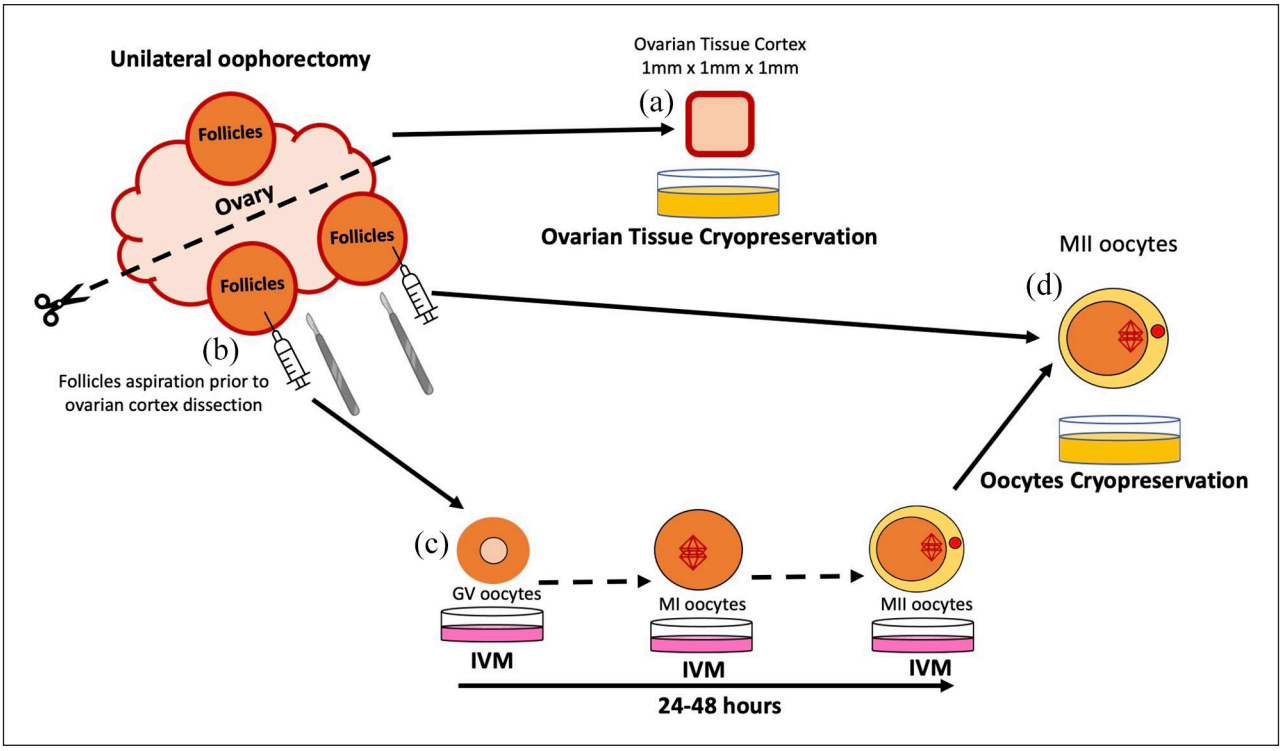


Figure 2. (a) OTC standard protocol—dissection of ovarian tissue fragment 1 cm^3 for cryopreservation. (b) Aspiration of visible follicles with needle or using scalpel to harvest possible oocytes before ovarian cortex dissection. (c) Immature oocytes (GV) harvest cultured with IVM media aiming for maturation (MII); at least 24–48 h as oocytes from OTC usually class 4–5 thus required longer IVM culture hours as compared to standard IVM. (d) Matured oocytes (MII) will be cryopreserved and use in future for IVF/ICSI.

embryo cryopreservation. Otherwise, most of the included studies in our review show that the OMR following IVM is at least 30%. Although in this review, the OMR is lower compared with the conventional IVM, it is immature because of the oocytes retrieved during OTC; follicles with a size of at least 5–10 mm represent class 3–5, whereas those with a size of 12–14 mm indicate class 6–7 in conventional IVM. The classes of oocytes had been established since 1986. The pre-antral follicle starting from 0.1 mm to ovulation follicle size of 20 mm indicates the class of oocyte maturation, in which the smaller follicle size indicates the lower class of oocytes, thereby representing the most immature stage of oocytes.[33]

Most IVM is used in NS cycles to tailor women with a higher risk of ovarian hyperstimulation syndrome (OHSS), such as those with PCOS. Early oocyte pick-up (OPU) in an ST cycle or before the growth of dominant follicles in NS follicles is recommended for this group of women. The idea of NS cycles was initiated by Cha et al.[14] in 1991, who successfully delivered triplets using NS oocyte donation. Subsequently, this strategy was expanded and combined with IVM, which led to a better outcome of using immature oocytes. In addition, IVM in an NS cycle has been proposed in cancer cases where stimulation is not permissible.[13] Therefore, in this cohort of patients, the cycles should be repeated to increase the number of oocytes within the same menstrual cycle.[34] However, the risk of failed oocyte maturation after 48 h of IVM culture is considered as a risk in NS cycles, which lead to low embryo yield with difficulty in recovering immature oocytes in follicles that are less than 9 mm.[35] Furthermore, this technical issue did not interfere with OTO-IVM.

During the standard OTC, most oocytes are harvested during medulla scrapping while processing the cortex layer to obtain at least 1–2 mm thickening, and all visible follicles can be aspirated directly prior to scrapping. The maturation of these oocytes will be assessed following IVM culture (Figure 2). As established, the size of follicles affects the classes of oocytes and their stage. However, the use of follicle size to predict the presence of oocytes remains unknown. Some aspirated follicles do not contain any oocytes upon examination under a microscope. The available evidence indicates that oocytes can be obtained in follicles that are more than 6 mm, and maturation is acceptable after 48 h regardless of the menstrual cycle phase during OTC.[21] Thus, follicle size should be observed during OTC and aspirated before tissue processing, or oocytes can be collected at the end of tissue processing. Then, these oocytes should be cultured with IVM as OTO-IVM.

On the contrary, the ovarian tissue will be transported to the embryology lab for processing during the standard

Table 3. The secondary outcome of fertilization rates following IVM.

Number	Author, year	Fertilization rates
1	Ingrid et al.[30]	76.9%
2	Gilad et al.[27]	*OC only*
3	Ingrid et al.[31]	65 ± 11%
4	Jens et al.[10]	*OC only*
5	Dmitry et al.[29]	*OC only*
6	Jack et al.[17]	*OC only*
7	Nathalie et al.[32]	*OC only*
8	Ettie et al.[28]	66.25%
9	Giovanna et al.[23]	50%
10	Maria et al.[21]	*OC only*
11	Giovanna et al.[22]	*OC only*
12	Yuval et al.[24]	*OC only*

OC: oocyte cryopreservation.

OTC procedure. Some literature shows that the risk of acute ischemia during this critical period can lead to oocyte degeneration; however, most of this evidence is obtained from animal studies.[36,37] Acute ischemia may be due to sudden loss of blood supply during oophorectomy and temperature changes during storage while transporting the tissue to embryology lab for OTC. In regard to the duration of oocyte maturation, our review revealed that although oocyte maturation is better in a shorter time, prolonged culture up to 48 h is acceptable, as it helps in yielding mature oocytes following the IVM culture.[22,38] The oocyte maturation outcomes either within less than 48 h or within 48 h are comparable. Thus, the proposed OTO-IVM environment with culture up to 48 h is acceptable to ensure that good numbers of mature oocytes are obtained following OTO-IVM.[38]

Using OC alone for FP, most OPUs are scheduled in an ad hoc basis without proper stimulation to cater to the limited period of FP treatment. Therefore, most patients undergo OPU following RS protocol regardless of the ovarian phase. Although it requires a higher dose of gonadotropin, the outcome of the luteal phase (LP) OPU is comparable to that of FPh, which is considered as the gold standard.[39] Regarding OTO-IVM, our review found that although LP OTO-IVM yields a lower number of oocytes than FPh OTO-IVM, the OMR and fertilization rates are comparable, although no stimulation is needed for this procedure.[28] Follicle development was better in the FPh, as an adequate amount of follicle-stimulating hormone and estradiol are present. Moreover, the production of these hormones is dormant in the LP because of the high level of progesterone.[40] However, this phenomenon was different as earlier evidence showed that possible mature oocytes could be harvested in LP OTO-IVM.[41] Previously, Hwang et al.[42] reported pregnancy after utilizing oocytes donated by a woman during her cesarean section. Since then, more evidence was gathered to consolidate that LP oocytes can be harvested and utilized. The anovulatory follicle theory within the LP postulates that certain follicles are developed until the late antral stage despite the high luteinizing hormone and progesterone levels.[43] In addition, priming with human chorionic gonadotropin can improve the maturation of FPh oocytes, but its role in small follicles in the LP is limited, which needs to be explored. Nonetheless, the maturation of oocytes with or without priming has acceptable fertilization rates.[44]

Following OTO-IVM, the ability of post-IVM oocytes during OTC to form euploid blastocyst remains unclear, although live births are reported worldwide.[45] As established, the intracellular maturation of oocytes is complex, and it depends on various regulators, including growth factors, gonadotropins, steroid, and sterols. Delineating the complex interaction between these positive and negative components is critical for determining the role that oocyte maturation plays in regulating follicle development and ovulation, which may lead to novel methods that can be used to modulate these processes in women with normal and aberrant fertility. In addition, the epidermal growth factor (EGF) is dependent on these hormones to produce essential proteins that balance the oocyte microenvironment.[46] An alteration of this condition leads to the non-synchronization of EGF network ligands and affects the overall quality of the oocytes. Thus, the oocyte maturation in the nucleus and cytoplasm must be archived.[47]

Given this complex mechanism, a possibly high developmental failure may be observed in post-IVM oocytes following ICSI/IVF. Most of the evidence highlights the occurrence of nuclear asynchrony and DNA fragmentation caused by inadequate culture duration, which interferes with oocyte competence and consequently leads to implantation failure and abortion.[46,47] However, these phenomena were also observed in non-IVM oocytes through the recent development of artificial intelligence with the combination of time-lapsed monitoring. This finding indicates that both oocytes, with or without IVM, are susceptible to developmental failure probably because of genetic factors rather than culture issue. Kirillova et al.[48] reported a euploid blastocyst formation following ICSI from oocytes obtained following OTO-IVM, leading to a better predictive of quality blastocyst following OTO-IVM. Her team then proposes the use of the biphasic IVM system for OTO-IVM. It portrays reasonable maturation rates following OTO-IVM compared with standard IVM, as it improves the molecular problems aiming at synchronizing nuclear and cytoplasmic maturation.[49] Thus, extrapolating from this evidence, the OTO-IVM can be implemented, as the current pregnancy rates following conventional IVM are reported to be up to 30%–40%.[45]

Limitation

Our review is limited to the role of OTO-IVM. Although our data quality is good based on NIH tool scoring (Table 1),

the IVM medium component was not explored in detail. The adjunct medium or hormone added to enhance IVM outcome (e.g. growth hormone) and the different techniques of oocytes following OTC were not discussed. Theoretically, additional hormone in different types or media influences the OMR, which needs to be further explored. Otherwise, the participants in this review are mostly post-pubertal; thus, evidence for the pre-pubertal group is limited. Finally, no clinical pregnancy rates are reported in this review, as in the oocytes and embryos were not utilized in this cancer cohorts.

Conclusion

Our findings indicate that OTO-IVM can increase the number of mature (MII) oocytes following OTC, and subsequently improve the FP strategy. Furthermore, OTO-IVM can be performed even without any stimulation and regardless of the menstrual phase, as the follicles size does not interfere with the number of oocyte yield, OMR, and fertilization rates. Nevertheless, the careful selection of patients with adequate culture time is essential. In the future, elucidating the microenvironment in post-IVM oocyte harvest during OTO-IVM can be explored to determine the molecular basis of competent oocytes following IVM and to improve assisted reproductive technology.

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Author contribution(s)

Ahmad Mohd Faizal: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.
Yodo Sugishita: Conceptualization; Formal analysis; Methodology; Validation; Visualization.
Yuki Suzuki-Takahashi: Formal analysis; Investigation; Methodology; Software.
Seido Takae: Investigation; Methodology; Resources; Supervision; Validation.
Hideyuki Iwahata: Conceptualization; Data curation; Investigation; Software; Supervision; Validation.
Yuki Horage-Okutsu: Investigation; Methodology; Validation.
Nao Suzuki: Conceptualization; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Supplemental material

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Ovarian Tissue Oocyte-*In Vitro* Maturation for Fertility Preservation

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Abstract

Mature oocyte vitrification is the standard of care to preserve fertility in women at risk of infertility. However, ovarian tissue cryopreservation (OTC) is still the only option to preserve fertility in women who need to start gonadotoxic treatment urgently or in prepubertal children. During ovarian cortex preparation for cryopreservation, medullar tissue is removed. Growing antral follicles reside at the border of the cortex-medullar interface of the ovary and are broken during this process, releasing their cumulus-oocyte complex (COC). By thoroughly inspecting the medium and fragmented medullar tissue, these immature cumulus-oocyte complexes can be identified without interfering with the OTC procedure. The ovarian tissue-derived immature oocytes can be successfully matured *in vitro,* creating an additional source of gametes for fertility preservation. If OTC is performed within or near a medical assisted reproduction laboratory, all necessary *in vitro* maturation (IVM) and oocyte vitrification tools can be at hand. Furthermore, upon remission and child wish, the patient has multiple options for fertility restoration: ovarian tissue transplantation or embryo transfer after the insemination of vitrified/warmed oocytes. Hence, ovarian tissue oocyte-*in vitro* maturation (OTO-IVM) can be a valuable adjunct fertility preservation technique.

Introduction

Fertility preservation (FP) options for women planned for gonadotoxic treatment, sex-reassignment therapy, or women who have a genetic predisposition for premature ovarian failure, depend on the health and age of the patient, available timeframe, type of treatment, patient's preference, and FP procedures available at the fertility center of choice. Vitrification of mature oocytes obtained after ovarian stimulation with gonadotropins and oocyte retrieval in a medical assisted reproduction (MAR) laboratory cycle is considered the preferred option for FP[1,2]. However, for prepubertal girls, women in whom the urgent start of gonadotoxic treatment or gonadectomy is required, or women with a high risk of permanent amenorrhea due to gonadotoxic treatment, a cycle of ovarian stimulation with gonadotropins is not possible, and ovarian tissue cryopreservation (OTC), which is an accepted and valid technique for FP[1,2,3], is the only option. The goal of OTC is to cryopreserve thousands of dormant primordial follicles in the ovarian cortex tissue, which can resume growth after the transplantation of frozen/thawed tissue onto the remaining ovary or in a peritoneal pocket after the careful screening of minimal residual disease in representative tissue fragments.

In order to obtain cortical fragments of 1-2 mm thickness suitable for cryopreservation, the soft medullar tissue needs to be removed. This medullar tissue typically entails growing follicles in various stages of development that escape the stiff ovarian cortex to allow for their growth and expansion[4]. For many years, several labs have been investigating the potential of these oocytes recovered from follicles residing in the remnant medullar tissue after ovarian cortical fragment preparation using *in vitro* maturation (IVM)[5,6,7], referred to as ovarian tissue oocyte IVM (OTO-IVM). Antral follicles, even those less than 6 mm in

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diameter, contain immature oocytes surrounded by cumulus cells that can mature, fertilize, and develop into healthy babies using an IVM system[8,9]. IVM is considered the standard of care for women at risk for ovarian hyperstimulation syndrome (OHSS), such as polycystic ovary syndrome (PCOS) patients. However, in the field of FP, there are limited data available for IVM in cases with a contraindication for ovarian stimulation; IVM of oocytes collected transvaginally is still considered innovative, and OTO-IVM is considered experimental[2,10]. That said, the reports of the first live births after OTO-IVM[11,12,13] highlight the potential of using OTO-IVM as an add-on technique when OTC is required for FP in patients[14].

This study provides technical details to adopt OTO-IVM in the MAR laboratory and illustrates the results obtained in a single center.

Protocol

The present study on OTO-IVM has been approved by the local Ethical Committee of UZ-Brussels (addendum of project 2008/068 and project 2022/303). All patients signed written informed consent. Each patient was individually assessed by a reproductive medicine specialist physician, navigator nurse, and the referring oncologist to compose the optimal FP treatment plan, taking into account the patient's preferences[14]. In short, patients eligible for OTC are in urgent need of FP and are less than 36 years of age[14]. To combine OTC with OTO-IVM, chemo- or radiotherapy cannot have been administered in the 6 months preceding OTC.

1. Laboratory environment and personnel

1. Perform OTC in a Class A laminar flow cabinet.
2. Perform OTC with two operators: one working aseptically in the laminal flow cabinet, and a second cleaning all non-sterile materials with a bactericide and sporicide decontaminant spray and handing over materials and supplies aseptically to the first operator. Process the ovarian cortex on a benchtop cooler lid (± 4 °C).
3. Perform the cumulus-oocyte complex (COC) search in a second laminar flow cabinet with a stereomicroscope in a MAR lab on a heated stage (37 °C).
4. Perform retrieval of the COC from the medullar remnants (sections 3 and 4) and initiate the IVM process (section 5). This is done by a third operator.

2. Media preparation

NOTE: Five types of media are used for this procedure (detailed below): OTC handling medium, OTC freezing medium, Search medium, LAG medium, and IVM medium. When preparing media, work aseptically in the flow cabinet, as detailed in section 1. Use new, unopened reagents for every procedure and maintain the sterility of all disposables used to ascertain the sterility of the produced media.

1. OTC handling medium
    1. Supplement Leibovitz's L15 medium with 4 mg/mL human serum albumin (HSA), 100 U/mL penicillin, and 100 µg/mL streptomycin (see **Table of Materials**).
    2. Keep the OTC handling medium refrigerated until use (for a maximum of 2 days).

        NOTE: Use OTC handling medium to rinse and process the ovarian tissue and use it cold (0-4 °C).
2. OTC freezing medium
    1. Supplement Leibovitz's L15 medium with 1.5 M dimethyl sulfoxide (DMSO) and 4 mg/mL HSA.
    2. Keep the OTC freezing medium refrigerated until use (for a maximum of 2 days).
3. Search medium

    NOTE: The Search medium (a HEPES-buffered medium for oocyte handling) is commercially available (see **Table of Materials**) and ready to use. Use the Search medium to rinse the filter and collect the COC while searching for COCs in between the medulla fragments (section 4).
    1. Fill six 14 mL round-bottom, sterile tubes with 6 mL of Search medium.
    2. Prepare a 4-well dish with 500 µL of Search medium covered with 350 µL of oil (see **Table of Materials**).
    3. Heat the tubes and the 4-well dish at 37 °C for at least 1 h prior to the arrival of the ovarian tissue. HEPES-buffered media do not require CO_2 incubation.
4. LAG medium

    NOTE: The commercially available IVM system (see **Table of Materials**) comprises two different media: LAG medium and IVM medium, which needs to be supplemented as detailed below. LAG medium is used to rinse the COCs, but can also be used for a 2-3 h incubation period preceeding IVM in IVM medium, as suggested by the insert of the IVM system.
    1. Use the commercially available, ready-to-use LAG medium (see **Table of Materials**).

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5. IVM medium
    1. Supplement commercially available IVM medium with 10 mg/mL HSA, 75 mIU/mL follicle stimulating hormone (FSH), and 100 mIU/mL human chorionic gonadotropin (hCG).
    2. Prepare a 4-well culture dish with one well of LAG medium and three wells of supplemented IVM medium: 500 µL of medium covered with 350 µL of oil overlay.
    3. Equilibrate the dish overnight in an incubator at 37 °C in 6% CO_2 and 20% O_2, the optimal environment for IVM culture.

3. Ovarian cortex preparation

NOTE: Laparoscopic whole ovary removal was performed as described by Jadoul et al.[15].

1. Upon arrival of the ovary in the laboratory, wash the ovary in the OTC handling medium (step 2.1) twice by transferring the ovary into a 100 mm Petri dish with the OTC handling medium.
2. With a scalpel, cut open the ovary in half longitudinally (**Figure 1A**).
3. Make several incisions in the medullar tissue both vertically and horizontally with a fresh scalpel. Avoid damaging the cortex. Pierce the firm antral follicles of various sizes within the medulla gently with the scalpel to release the follicular fluid in the OTC handling medium.
4. Pare down the soft medulla tissue with surgical scissors (**Figure 1B**). This procedure may take several minutes.
5. Put the ovarian shell in a new dish with fresh OTC handling medium during the trimming process.
6. Transfer the dish with medullar fragments and released follicular fluid (**Figure 1C**) to the second flow cabinet to start the search for COCs.
7. Repeat steps 3.4 to 3.6 until the desired thickness (1-2 mm) of the cortex tissue is obtained.
8. Slice the cortex into pieces of approximately 8 mm x 5 mm.
9. Incubate the pieces 3x consecutively for 10 min in approximately 25 mL of OTC freezing medium (step 2.2) in 100 mm Petri dishes.
10. Place one piece in 800 µL of OTC freezing medium in a cryovial.
11. Cryopreserve the ovarian tissue using a slow freezing protocol in a cryochamber controlled by a temperature controller (see **Table of Materials**): from 4 °C to -7 °C at -2 °C/min, manual seeding at -7 °C, from -7° C to -40 °C at -0.3 °C/min, from -40 °C to -100 °C at -10 °C/min, and at -100 °C plunge the cryovials in liquid nitrogen and store them.

4. Search for COCs

1. Prepare the laminar flow cabinet for the COC search.
    1. Warm 60 mm culture dishes on the heated stage under the stereomicroscope in the laminar flow cabinet.
    2. Put the 14 mL tubes with 6 mL of preheated Search medium (step 2.3.1) in a heated block, and the preheated 4-well dish with Search medium on the heated stage under the microscope in the laminar flow cabinet.
    3. Place a sterile filter (cell strainer, 70 µm mesh size; see **Table of Materials**) bottom-down in a culture dish.
    4. Take a 290-310 µm glass capillary for use: do not use smaller capillaries than 290-310 µm, in order to avoid damage to the oocyte-cumulus cell connectivity.
    5. Ensure 1 mL filter tips and a 1 mL pipet are available.
2. Take the first dish with medullar fragments from the OTC laminar flow cabinet (4 °C) and put the dish on the heated stage (37 °C) in the IVM laminar flow cabinet as soon as possible.

    NOTE: The first dish of medullar fragments and follicular fluid might be contaminated with blood from blood-filled ovulated follicles or the vasculature of the ovary itself. Red blood cells blur clear vision and complicate the search for COCs. The contaminated medium must be removed to wash away the red blood cells (see step 4.3).

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3. Remove the blood cell contamination by following the steps below.
    1. Pipet 2 mL of Search medium over the filter membrane (70 µm cell strainer) to wet the membrane and put the dish, which captured the medium, aside on the heated stage.
    2. Flip the filter upside-down and place it with the handle against the rim of a new culture dish, creating a slope with the bottom of the filter.
    3. Collect blood-contaminated medium in between medullar fragments using a 1 mL tip and blow it gently over the filter membrane (**Figure 1D**) to capture the COCs present in the contaminated medium.
    4. Repeat step 4.3.3 until most of the blood-contaminated medium is removed.
    5. Pour fresh Search medium over the medullar fragments immediately to keep the COC suspended in the culture medium at all times.
    6. Rinse the sloped filter membrane gently with 2 mL of Search medium to rinse away red blood cells on the filter membrane.
    7. Place the filter bottom-down in a new dish and pour 3-4 mL of Search medium into the filter to expel the COC from the filter membrane into the medium that fills the dish. Remove the filter. To ensure that the filter membrane does not dry out (and any possible COCs that are not yet expelled from it), immerse the filter bottom-down in the first dish, which was used to wet the filter for the first time.
    8. Immediately examine the expelled medium for COCs by visual inspection under a stereo microscope with a magnification of 10x-50x. Search for clear translucent oocytes with a rim of dark, compact surrounding cumulus cells (**Figure 1E**). Swirl the medium in the dish and examine the medium again.
    9. Rinse the filter a second time in a new dish and examine the expelled medium for COCs.
    10. Examine the medium in the dish where the filter is immersed for the remaining COCs.
    11. Transfer COCs with a glass capillary to the 4-well dish containing the Search medium (**Figure 1E**). Keep the dishes on the heated stage at all times.
4. Search in between the medullar fragments for COCs after removing the contaminating blood cells from the dish with medullar fragments and replenishing the dish with clear Search medium. Use the glass capillary to move around the medullar fragments and swirl the medium in the dish in order to find COCs. Pull apart large medullar fragments with tuberculin needles on a 1 mL syringe if the presence of an oocyte is suspected.
5. Collect all intact COCs in the 4-well dish with Search medium.

    NOTE: In a typical OTC procedure, cortex tissue is pared down from the medulla using three consecutive 100 mm dishes, where the ovarian shell is moved to a new dish with fresh medium and where the remnants are transferred to the IVM flow for COC search. Usually, only the first dish requires the removal of blood cells; in the second and third dishes, fewer medullar fragments are present, and COC search is performed directly in between fragments and in the medium.

5. IVM of COCs

1. Rinse the COCs in a clean well with Search medium.
2. Move the pre-equilibrated IVM culture dish (the 4-well dish that contains one well of LAG medium and three wells of IVM medium) from the incubator to the heated stage in the IVM flow cabinet.
3. Label the IVM culture dish containing COCs with patient information.
4. Rinse the COCs in LAG medium (2-3 s) and place them in one of the three wells with supplemented IVM medium. Culture the COCs in groups of approximately 10 COCs per well. Omit naked oocytes-oocytes devoid of attached cumulus cells-from the culture, as they are known to have severely compromised developmental potential.
5. Place the dish in an incubator at 37 °C, 6% CO_2, and 20% O_2 for 30 h.

6. Handling mature oocytes

1. Strip oocytes of their surrounding cumulus cells by brief exposure to 80 IU of hyaluronidase (see **Table of Materials**) and gentle mechanical pipetting after 30 h of IVM.
2. Identify mature oocytes by the extrusion of the first polar body.

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3. Vitrify or inseminate the mature oocytes, depending on the patient's preference.

   NOTE: If the maturation check after 30 h of IVM falls outside the acceptable working hours, the IVM duration can be shortened to 28 h or extended up to 42 h. If only a few mature oocytes are obtained after 30 h, immature oocytes can be cultured additionally overnight in the original IVM well, devoid of cumulus cells, and used the next morning for vitrification or intracytoplasmic sperm injection (ICSI) when mature.

Results

Over the past decade, 98 patients undergoing oophorectomy or ovarian biopsy for OTC were also offered OTO-IVM. The results presented here are an update of the clinical program as published before[7,13]. Immature oocytes obtained during ovarian tissue processing were matured *in vitro* predominantly for 30 h. However, a more flexible maturation time was allowed for practical reasons or because of low maturation, ranging from 28-42 h. Patients opted predominantly for oocyte vitrification (85/98) or-upon specific request of the patient-embryos were created by inseminating mature oocytes and embryo vitrification (13/98). A total of 1,417 oocytes were collected in 98 patients aged between 1 and 38 years old who were offered OTC with OTO-IVM. The mean oocyte maturation rate was 40% ± 22% (mean ± SD). The mean maturation rate was lower in prepubertal girls compared to postpubertal women (26% vs. 42%, respectively; **Table 1**). For 94/98 patients, immature oocytes were found, and at least one metaphase II (MII) was obtained for 86/94 patients after OTO-IVM, indicating that OTO-IVM provided an additional benefit of mature oocytes for cryopreservation in 88% of the OTC population.

Overall, an average of 6.0 ± 6 mature oocytes was obtained in the OTC population (intention to treat, ITT). However, some patients were very young (<5 years old; n = 4) or had a limited amount of ovarian tissue available for OTO-IVM (ovarian biopsy [n = 4] or tumor involvement in the ovary [n = 4]). If only patients with successful OTO-IVM were considered (at least one MII; n = 86), an average of 6.5 ± 6 MII was obtained.

In order to preserve the fertility chances of women, oocyte vitrification was advised for the patients. However, for 13 patients, the couple insisted on creating embryos for FP. Fertilization success was assessed by the presence of two pronuclei (2PN) at approximately 18 h after ICSI. OTO-IVM oocytes showed a 63% fertilization rate (40 2PN/64 MII); 68% of the zygotes developed into cleavage stage embryos of sufficient quality for cryopreservation (27 good quality embryos [GQE]/40 2PN), generating on average 2.1 ± 2 embryos per patient being vitrified. In brief, GQEs sufficient for cryopreservation are defined as six cells or more and a maximum of 20% fragmentation[7].

Data on the warming of OTO-IVM oocytes or embryos are scarce. Of 86 patients with cryopreserved gametes/embryos, 17 patients returned to the MAR clinic with a desire for pregnancy. Ten decided to use their cryopreserved material obtained after OTO-IVM; seven patients showed sufficient ovarian activity to start an *in vitro* fertilization (IVF)/ICSI stimulation cycle with fresh oocytes. Five patients had OTO-IVM oocytes warmed, with a survival rate of 75% (58/77). These oocytes showed a similar potential for fertilization (48%; 28/58) compared to fresh OTO-IVM oocytes, but a lower embryo development rate, generating only 29% (8/28) GQEs for transfer or cryopreservation, an average of 1.3 ± 1 per patient. Out of eight created embryos, seven were warmed, of which six embryos did not lead to pregnancy, and one embryo led to a healthy live birth.

For five patients, OTO-IVM embryos were warmed. A total of nine embryos were warmed, of which one did not survive, two were genetically tested for breast cancer (BRCA) genes and considered unsuitable for transfer, four did not lead to a pregnancy, and two embryos led to two healthy babies born in two patients.

Overall, three of the 10 patients who returned to the MAR clinic with a desire for pregnancy had a healthy baby with their cryopreserved OTO-IVM material (30%), without the need for additional laparoscopic surgery for tissue transplantation and the risk of reintroducing malignancy.

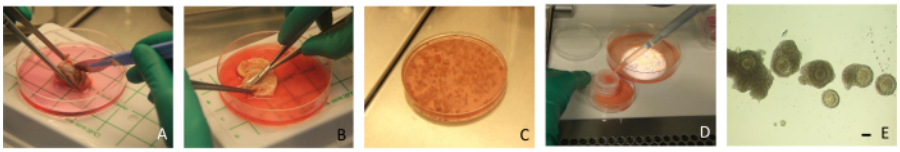


Figure 1: Ovary incision and isolation of ovarian cortex and COCs. (**A**) Longitudinal incision of the ovary through the cauterization lesion to cut the ovary in half. (**B**) Removal of the inner medullar tissue to isolate the cortical ovarian tissue with scissors. (**C**) Medullar fragments and follicular fluids remaining after ovarian cortex isolation. (**D**) Filtration of the medium through a 70 µm mesh filter to isolate COCs and remove contaminating red blood cells. (**E**) Representative image of a COC before IVM; scale bar corresponds to 100 µm. Please click here to view a larger version of this figure.

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ITT	Total	Prepubertal	Adult
n	98	11	87
average # Cortex fragments/patient	18.5 ± 10	11.5 ± 7	19.4 ± 10
average # COC/patient	14.5 ± 12	16.2 ± 16	14.2 ± 12
average # MII/patient	6.0 ± 6	4.3 ± 5	6.2 ± 6
total # COC	1417	178	1239
total # MII	563	47	516
MII rate	40%	26%	42%

Table 1: The outcome of OTO-IVM in the total population and stratified according to menarche. Abbreviations: ITT = intention to treat; n = amount of subjects; COC = cumulus oocyte complex; MII = metaphase II oocyte.

Discussion

The priority of the FP procedure is always to manipulate and freeze the ovarian cortex according to the standard operating protocol that has been validated in the clinic. A drawback in FP is the absence of a standard protocol available in the published literature regarding OTC and OTO-IVM. It is difficult to assess the efficiency and validity of the techniques and adaptations since there is a large time gap between freezing/vitrification and thawing/warming in a clinical setting. If changes to the OTC protocol are made to augment the efficiency of OTO-IVM, it is vital to validate the adapted OTC protocol for tissue health upon cryopreservation and thawing. In this report, the protocol for OTC, routinely used at Brussels IVF at the University Hospital of VUB, Brussels, prescribes that the medulla is pared down from the ovarian cortex using scissors. As such, medullar tissue is systematically cut into small fragments, and COCs are set free. Other labs prepare the ovarian cortex using scalpels, where the bulk of the medullar tissue is scooped from the cortex shell. Here, additional cutting of the large medullar piece is needed to release the COC. Puncturing visible, large antral follicles with a needle upon receiving the ovary in the laboratory is contraindicated, as these punctures damage the ovarian cortex. Secondly, the yield of COC aspiration from large antral follicles in an ovary *ex vivo* is low.

If ovarian tissue is transported from a local hospital to a center of expertise for tissue cryopreservation, this transport is performed under cold conditions (0-4 °C) for up to 24 h with minimal tissue damage[16]. During transport, the ovary is suspended in saline solution, phosphate-buffered saline, or more complex media like Leibowitz's L15, alpha modification of Eagle's medium, or Custodiol; however, data about tissue viability (and OTO-IVM success) related to different transport media are scarce[16]. The OTC protocol states that the ovarian cortex should be processed at 0-4 °C to slow metabolism and reduce ischemic damage. However, chilling oocytes influences their cytoskeletal conformation[17] and membrane integrity[18], and impairs the maturation potential of ovarian tissue-derived oocytes[19] (immediate processing at 37 °C results in 42% MII, whereas transport for 2-5 h on ice reduces the MII rate to 27%[19]). Other centers perform ovarian tissue processing at room temperature or 37 °C, but the presented results reflect tissue processing in cold conditions with intermittent transport of medullar fragments and medium to a 37 °C heated stage for COC search.

For IVM the standard protocol, used for infertility patients with a PCOS background, was used[9]. A commercial IVM medium is used to culture immature oocytes, where the manufacturer recommends supplementing the IVM medium with maternal serum. In order to avoid bias of unknown substances delivered by maternal serum, the currently presented IVM results are obtained using commercial HSA as the protein source in the IVM medium. Novel biphasic IVM culture systems have been developed, which augment the yield in mature oocytes in an infertile PCOS population[20] as well as in OTO-IVM[21]. The continued efforts in optimizing IVM protocols will likely enhance, also the efficiency of OTO-IVM in fertility preservation patients. Immature oocytes are incubated at 20% O_2 during the maturation phase, unlike incubation

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under 6% O_2 for embryonic preimplantation development. IVM in reduced oxygen conditions impairs blastocyst development[22], hence it is critical to perform the 30 h incubation period in IVM medium in 20% O_2. Maturation is assessed after 30 h by the enzymatic and mechanical removal of surrounding cumulus cells. Sometimes, an additional overnight culture in IVM medium of cumulus-free oocytes was applied to increase the yield of mature oocytes; However, only a limited amount of additional mature oocytes were obtained after this prolonged maturation time. Mature oocytes were cryopreserved using the standard protocol for oocyte vitrification at Brussels IVF[23].

As shown in the results, OTO-IVM can be offered to most patients undergoing OTC; however, for patients under 5 years of age, the likelihood of obtaining oocytes is low[7] due to the limited differentiation between cortex and medulla tissue and the absence of antral follicles. In general, maturation rates of OTO-IVM are lower for children as compared to adults, most likely due to the intrinsic differences between adult and prepubertal folliculogenesis and hence the compromised developmental capacity due to, for example, increased aneuploidy[24,25]. Similarly, advanced age (>30 years) has been described to affect the OTO-IVM maturation rate[25]. Further, when ovaries have cysts or malignant involvement, the yield after OTO-IVM can be low[26], as is also seen when an ovarian biopsy is taken instead of a whole ovary. The selection of patients for OTO-IVM is important in determining successful outcomes.

A subset of FP patients have a contraindication for ovarian tissue transplantation (high risk of reintroducing malignant cells in, for example, ovarian cancers) or host-hostility in autoimmune diseases, and need to wait until human *in vitro* folliculogenesis is clinically applicable to have their genetically-own child. OTO-IVM is the only clinically applicable FP option for these patients.

Although the clinical relevance of OTO-IVM is evident, some issues need to be solved to validate this technique before the experimental label of the technique can be lifted. The impact of the temperature of transport and processing requires investigation in more detail. The standard IVM protocol used for infertile patients may not be efficacious for immature oocytes harvested from ovarian tissue, and IVM culture media and methods require finetuning to enhance oocyte quality after maturation. The lower oocyte quality of OTO-IVM oocytes is illustrated by a lower survival rate after vitrification/warming of OTO-IVM oocytes (75%), as compared to mature oocytes harvested after ovarian stimulation in an oocyte donation program (93.7%)[23]. More data on oocyte vitrification efficiency and the developmental capacity of OTO-IVM oocytes are necessary to estimate the true potential of OTO-IVM in FP. The population of patients who are suitable for oophorectomy/ovarian biopsy for FP is shrinking, as a result of the advances in therapeutical agents rendering cancer therapies more efficient and less gonadotoxic.

In conclusion, performing OTO-IVM creates an additional option for FP and offers a realistic additional chance of achieving pregnancy, as shown by the three healthy children born in three individual patients in this small cohort of 10 patients who warmed their cryopreserved OTO-IVM oocytes or embryos. Therefore, OTO-IVM is considered a valuable add-on tool that can be used when cryopreservation of ovarian tissue is the best approach for preserving a patient's fertility.

Disclosures

The authors have no competing financial interests.

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Fertility preservation in patients with medical indications: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Washington, D.C.

Patients preparing to undergo therapies that pose a risk to their fertility or who are at risk of premature ovarian insufficiency should be provided prompt counseling regarding available options for fertility preservation. Fertility preservation can best be provided by comprehensive programs designed and equipped to confront the unique challenges facing these patients. This document replaces the document entitled "Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion," last published in 2019. (Fertil Steril® 2026;125:247–59. ©2025 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Fertility preservation, premature ovarian insufficiency, infertility, reproductive endocrinology

Systemic therapy, radiation therapy, and surgery for medical conditions in children, adolescents, and adults of reproductive age can harm future fertility. Moreover, some medical conditions increase the risk of premature gonadal failure. Fertility preservation strategies have been shown to be effective in decreasing infertility risks in these populations.

Utilization of fertility preservation services remains low and is related to social determinants of health, despite increasing health insurance coverage, awareness among clinicians and patients, and availability of fertility preservation programs (1). This document summarizes components of comprehensive fertility preservation care and provides specific clinical recommendations on the basis of currently available strategies.

COMPONENTS AND FUNCTIONS OF A FERTILITY PRESERVATION PROGRAM

Clinics offering fertility preservation should have the expertise and infrastructure to provide timely interventions. Table 1 lists the components of a comprehensive fertility preservation program. Timely initiation of reproductive risk counseling by the primary medical team and rapid referral to a reproductive specialist for fertility preservation consultation is central. When appropriate, safe, and efficient completion of fertility preservation treatment should take place, followed by post-treatment counseling and documentation (Fig. 1). Financial navigation is a key component. Programs unable to provide specific components of fertility preservation services should still counsel patients about all options and provide timely referrals to programs with needed resources.

REPRODUCTIVE RISK AND FERTILITY PRESERVATION OPTIONS COUNSELING

Patients should be counseled on known and unknown reproductive risks of planned medical treatments. The risk of future infertility and secondary hypogonadism varies on the basis of the disease and treatment regimen and may not be fully known at the time of counseling. The safety of future pregnancy in females should be addressed. Counseling of patients considering fertility preservation should include a discussion of relevant treatments and alternatives, including expectant management, potential use and efficacy of future fertility treatments, use of donor gametes or embryos, adoption, and living child-free. The patient's current state of health must be considered, as some may be too ill to safely undergo fertility preservation. A team approach to patient counseling is recommended. As time permits, patients may meet with physicians, nurses, and mental health professionals to discuss decisions. This allows for a more comprehensive evaluation to explore and understand the psychosocial and medical needs of each patient.

Consent and disposition

In patients who cryopreserve gametes, embryos, or tissues, disposition in the event of death should be discussed and documented, and minors should reconsent once they become adults. It is important for clinics to specify

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TABLE 1

Components and functions of a comprehensive fertility preservation program.

Component	Activities	Personnel
Fertility preservation team identification	Select feasible activities, personnel to support them, and generate standardized processes: • Expedite referral to fertility specialist • Counsel on known and unknown reproductive risks from medical treatment or condition • Counsel on (tailored) options for fertility preservation, storage, potential need for a gestational carrier, and disposition of reproductive materials/tissues • Counsel patients on heritable disease and potential for gametes to carry mutations/discuss preimplantation genetic testing • Determine who needs FDA testing • Perform fertility preservation procedures • Perform fertility preservation laboratory procedures: oocyte/sperm/embryo/gonadal tissue cryopreservation • Counsel on financial costs, insurance coverage, and philanthropic programs • Assist patients in accessing insurance and philanthropic programs • Coordinate care among primary medical and fertility preservation teams • Identify and refer to outside facilities for fertility preservation services that cannot be provided locally	Fertility program administrators Fertility specialist for females and males (reproductive endocrinology, urology, and reproductive surgeon) Fertility preservation navigator Fertility nursing Assisted reproductive technology and andrology laboratory Financial team Mental health clinicians Social workers Genetic counselors Maternal fetal medicine specialists Legal experts Ethics
Patient identification process	Collaborate with medical teams that have patients who need medically indicated fertility preservation Decide on strategies to identify patients consistently • Set criteria for eligible patients • Determine the best process for identification, e.g., EHR best practice alerts, new patient checklist Referring to clinician education sessions on patient identification	Fertility specialist Fertility preservation navigator Primary medical team champion
Patient referral process	Decide on strategies to refer patients consistently • Single point easy access • Fertility preservation team e-mail and consult phone number • EHR enabled urgent referrals to fertility preservation team Coverage of referrals on weekends and holidays Referring to clinician education sessions on patient identification	Fertility specialist Fertility preservation navigator Fertility preservation program administrators Primary medical team champion EHR team
Financial support for fertility preservation	Contract with health insurance plans to provide patients with in-network clinicians, laboratories, and facilities Train the financial team on medical and pharmacy benefit verification, preauthorization, escalation to insurance plan supervisors, and appeals Identify state-level appeal processes with insurance regulators Generate appeals letter templates Assess feasibility of decreasing upfront, out-of-pocket costs Identify loan and philanthropic programs Generate patient-facing materials for cost-sharing estimates, loan and philanthropic programs, and insurance navigation	Fertility preservation navigator Financial team Social worker
Educational materials for patients	Find/develop health literacy appropriate • Website • Handouts a. Reproductive risks b. Fertility preservation procedures c. Next steps	Fertility specialist Fertility preservation program administrators

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TABLE 1

Continued.

Component	Activities	Personnel
Quality improvement	Review the fidelity of fertility preservation program Provide feedback Adapt the program for improvement	Fertility preservation program administrators

FDA = Food and Drug Administration, EHR = electronic health record.

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where gametes/embryos will be stored and for how long (2). Patients benefit from anticipatory guidance on the potential limits and restrictions on stored materials, including state laws, regulations for transfer, and clinic policies restricting acceptance of outside tissues (3, 4). The possibility of using a gestational carrier should be addressed, particularly for patients who may not be able to carry an autologous pregnancy because of effects of therapy, ongoing treatments, or health (5).

EFFECTIVE FERTILITY PRESERVATION STRATEGIES FOR FEMALES

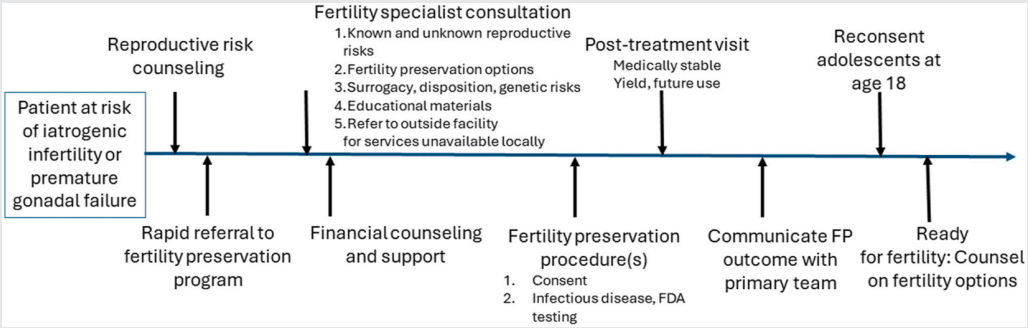
Mature oocyte cryopreservation

For postpubertal females, mature oocyte cryopreservation is an established fertility preservation technique. This process requires controlled ovarian stimulation (COS), that is, stimulating the ovaries with gonadotropins, and surgically retrieving oocytes, which are then cryopreserved. Oocyte cryopreservation allows for the future choice of sperm source and control of disposition. Cryopreservation of oocytes rather than embryos should be on the basis of patient choice. Patients should be advised that oocyte cryopreservation allows them to choose the sperm source in the future and allows them alone to control the disposition of the frozen eggs. Data on pregnancy and live birth rates from oocyte cryopreservation in medically indicated fertility preservation are scarce. Age at vitrification and the number of oocytes are predictors of future success (6, 7). One study found a 35% live birth rate in 80 oncofertility patients who returned to use their vitrified oocytes, a rate similar to patients who underwent planned oocyte cryopreservation (6). Patients should be thoroughly counseled about success rates given a patient's age and the number of oocytes cryopreserved, using clinic-specific success rates whenever possible. Although data on live birth rates from banked oocytes in specific, medically indicated fertilization preservation populations are limited, available data from patients who underwent oocyte cryopreservation for nonmedical indications may help guide counseling (8).

Embryo cryopreservation

Embryo cryopreservation using partner or donor sperm is an established fertility preservation technique that offers a more predictable likelihood of success on the basis of the number and quality of embryos stored. This process involves COS and surgically retrieving oocytes, which are then inseminated and cryopreserved. The stage at which to cryopreserve embryos depends on clinic-specific protocols and individualized patient counseling. Patients should be thoroughly counseled about success rates given a patient's age and the number and stage of embryos cryopreserved using clinic-specific rates whenever possible. Although data on live birth rates from banked embryos in specific, medically indicated fertility

FIGURE 1



Key processes in the patient journey for medically indicated fertility preservation and family building.

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preservation populations are limited, available data from infertile and donor populations can be used for counseling (9).

Role of genetic testing in embryo cryopreservation

Patients seeking embryo cryopreservation may be candidates for preimplantation genetic testing (PGT). Preimplantation genetic testing for monogenic disorders (PGT-M) may be offered to patients with known mutations that predispose them to cancer or other serious conditions (10). Patients diagnosed with hereditary cancers after urgent embryo cryopreservation may have embryos thawed and biopsied for testing (11, 12). Preimplantation genetic testing for aneuploidies (PGT-A) may be considered in select patients expected to have multiple embryos available for cryopreservation and who are of advanced reproductive age and/or plan to use a gestational carrier. Patients should be counseled that performing PGT will reduce the number of available embryos to transfer and that data do not support the routine use of PGT-A in in vitro fertilization (IVF). Clinicians should engage in shared decision-making with patients to tailor the fertility preservation strategy (13).

Ovarian stimulation for embryo or mature oocyte cryopreservation

Controlled ovarian stimulation for embryo or mature oocyte cryopreservation remains the most likely strategy to result in subsequent pregnancy. This procedure should be recommended as long as the patient's medical condition safely allows COS, there is adequate time, and there is a reasonable chance of response and oocyte retrieval.

Immediate start, random start, and duo-stimulation

To expedite fertility preservation, stimulation may be started immediately with antagonist-based protocols without regard to the phase of the menstrual cycle (immediate or random-start COS) (14). The trigger medication should be guided by the clinical scenario and may be human chorionic gonadotropin (hCG) only, dual trigger, or gonadotropin-releasing hormone agonist (GnRHa) only to minimize the risk of ovarian hyperstimulation syndrome (OHSS) (15). Compared with conventional stimulation, immediate-start stimulations result in negligible delays and have similar embryological and pregnancy outcomes (16, 17). Despite limited time, it is important to procure a sufficient number of oocytes to maximize the chance of a successful future pregnancy (18). Multiple ovarian stimulations may be possible and should be considered. Indications for multiple stimulations may include poor outcomes from the first cycle, advanced age, and/or intended PGT-M. If time allows, duo-stimulation may shorten the window from one stimulation to the next (19). Stimulation may occur before systemic therapy, before and after surgery, and in some scenarios while on adjuvant endocrine therapy. Financial and time constraints may preclude multiple cycles.

Posttreatment mature oocyte or embryo cryopreservation

Fertility preservation after treatment may be considered in some patients. Candidates include patients who have been exposed to medical treatments that increase the risk of premature ovarian insufficiency or infertility and who subsequently have a residual but narrower window of remaining ovarian function, as well as patients who completed fertility preservation but have insufficient cryopreserved materials for a reasonable chance at achieving their goals for family size.

In general, stimulation during or immediately after gonadotoxic treatments is not recommended. Animal data suggest that there may be an increased risk of miscarriage and birth defects (20). After gonadotoxic treatments, the probability of cycle cancellation is higher, and the number of oocytes retrieved, number of embryos, and successful pregnancies are lower when compared with individuals without prior gonadotoxic treatments (21). A case series reported stimulation between cycles of chemotherapy in four patients with hematologic malignancies yielded no follicular development ($n = 2$), no oocytes ($n = 1$), or low embryo development ($n = 1$) (22). Case reports of stimulation after and before hematopoietic stem cell transplant in patients with acute myeloid leukemia have reported successful ovarian stimulation with mature oocyte and embryo freezing (23, 24). There are no human studies that have specifically examined the quality of oocytes and embryos that result after a recent course of chemotherapy. It is known that chemotherapeutic agents can cause deoxyribonucleic acid (DNA) abnormalities, as well as oxidative damage, in somatic and germ cells (25, 26). In mice, conceptions that occurred within 3 months of exposure to cyclophosphamide resulted in a higher rate of pregnancy failures and fetal malformations (20). Although oocytes and embryos can be frozen and PGT-A performed, it is notable that transfer outcomes have not been reported, and PGT-A does not identify mutagenesis, so patients should be counseled accordingly. A safe interval for offspring health between completion of chemotherapy and oocyte or embryo cryopreservation has not been established.

The long-term optimal timing for ovarian stimulation for fertility preservation is unclear. Using antimüllerian hormone (AMH) as a measure of recruitable ovarian follicle pool, an overall postchemotherapy treatment trajectory shows increasing AMH levels for 2–3 years before plateau. These data suggest that for patients with residual ovarian reserve, peak oocyte yield would be highest when AMH plateaus after treatment (27). Prospective cohort studies are needed for validation. Studies examining pregnancy outcomes in cancer survivors remote from therapy have reported no significant increase in congenital malformations, genetic abnormalities, or malignant neoplasms in the resulting offspring (28–31).

SAFETY CONSIDERATIONS

Medically complex patients

Patients facing fertility-threatening treatments for malignancies or other systemic conditions often have underlying

comorbidities that increase the risk and complexity of fertility preservation (32). Fertility clinics differ in their ability to care for medically complex patients; thus, careful consideration must be taken when planning fertility preservation treatments. For example, patients with cardiovascular and airway risks (example: mediastinal masses) require anesthesia evaluation for potential modifications to anesthetics (example: local anesthesia without deep sedation), or procedures may need to be performed in a hospital setting rather than an ambulatory surgicenter. For pediatric patients, state and surgery center regulations may require pediatric advanced life support certification.

Depending on tumor location, patients may require nonvaginal oocyte retrieval approaches, including abdominal, transvesical, or laparoscopic. Patients with abnormal hematologic parameters at risk for hemorrhage or thrombosis may also need special care, including blood products, tranexamic acid, and anticoagulation. Multidisciplinary collaboration with the patient's medical providers is recommended.

Prevention of ovarian hyperstimulation syndrome

The impact of OHSS can be profound in medically complex patients, with the potential to delay planned therapy. Therefore, the use of appropriate strategies to reduce the risk of OHSS may be particularly valuable, including antagonist cycles, dosing gonadotropins to ovarian reserve, lowering the starting gonadotropin dose, using gonadotropin-releasing hormone (GnRH) agonist to trigger oocyte maturation, using a lower dose of hCG to trigger oocyte maturation (without definitive evidence of reducing OHSS), and starting a dopamine agonist on the day of hCG trigger. In letrozole ovarian stimulation cycles, follicle number should be used to choose strategies for reducing OHSS risk, because estradiol levels, masked by letrozole, remain low (15).

Cancer outcomes

The long-term safety of ovarian stimulation in the setting of cancer, notably in estrogen receptor-positive (ER+) cancer or breast cancer gene positive (BRCA+), is reassuring. Several observational studies in the setting of breast cancer show no differences in recurrence and/or disease-free survival (33–35). In addition, a limited dataset suggests ovarian stimulation has no impact on pathologic complete response in a neoadjuvant setting (36). In these studies, concomitant estrogen modulation was administered during ovarian stimulation with use of an aromatase inhibitor or tamoxifen, and therefore, its use is encouraged.

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation is an acceptable technique and is no longer considered experimental. (37, 38). Cryopreservation of ovarian cortical tissue represents a way of preserving thousands of ovarian follicles at one time. This technique is recommended for patients facing highly gonadotoxic therapies who cannot delay cancer treatment to undergo ovarian stimulation and oocyte retrieval, and for prepubertal patients because there is limited experience with ovarian stimulation for mature oocyte cryopreservation before puberty (39, 40). In addition, it may be offered as an additional fertility preservation strategy for high-risk patients who have undergone other fertility preservation procedures.

Ovarian tissue cryopreservation involves obtaining ovarian cortical tissue before ovarian failure by laparoscopy or laparotomy, dissecting the tissue into small fragments, and cryopreserving it using either a slow-cool technique or vitrification. On the basis of current evidence, removal of both ovaries for cryopreservation is not justified at this time, unless the chemotherapy regimen has a high likelihood of inducing complete ovarian failure. After the treatment, patients with infertility or ovarian failure can undergo ovarian tissue transplantation orthotopically or heterotopically. Orthotopic transplantation has been the most successful method for using ovarian tissue, with only one live birth reported after heterotopic transplantation (41). Various surgical techniques have been utilized for transplantation, including transplantation into the existing ovary, under a peritoneal pocket in the pelvic side wall or abdominal wall. According to a 2022 systematic review, there have been at least 189 live births after autologous allogeneic ovarian tissue transplantation (42). Transplantation of previously cryopreserved ovarian tissue resulted in a 37% pregnancy rate and a 28% live birth rate. According to this study, 69% of pregnancies were conceived without assistance. Over 70% of patients had resumption of ovarian function at a mean time of 19 weeks posttransplant, lasting an average of 2.5 years (42–45). Thus, it is unlikely that ovarian tissue transplantation is effective for preservation of long-term endocrine function and should generally be performed to promote fertility when patients are ready to conceive.

Before undertaking ovarian tissue cryopreservation or transplantation, consultation with the patient's medical oncologist is appropriate to understand risks related to transplantation and potential options for tissue screening (46, 47). Where cancer cells may be present in ovarian tissue, it is unclear whether screening with histologic evaluation or with tumor markers is reliable and reduces the risk of reseeding tumor cells (48). One case of recurrent cancer has been reported posttransplant in a patient who had ovarian tissue frozen/transplanted in the setting of an ovarian granulosa cell tumor (42). Although there has been particular concern related to transplantation in patients with leukemia undergoing ovarian tissue cryopreservation, recent literature suggests that transplantation of ovarian tissue in leukemic patients may be safe in patients whose tissue was removed after receiving high-dose, preconditioning chemotherapy before stem cell transplantation (49). There have been 18 reported transplants in leukemic patients with nine resulting in live births, and there have been no cases of recurrence (49).

Cumulus oocyte complexes may be aspirated from small follicles or identified during ovarian tissue dissection and processing. These oocytes may be matured in vitro and cryopreserved before or after fertilization. This approach may be advantageous because it provides additional oocytes or embryos for cryopreservation, without additional delay.

Importantly, it offers patients the potential for pregnancy without ovarian tissue transplantation, which could pose a risk of reintroducing cancer cells in certain circumstances. A few live births have been reported in patients who underwent in vitro maturation of oocytes from ovarian tissue (37, 38, 50). Although in vitro maturation may be a reasonable approach to fertility preservation in some situations, outcome data are limited, and more established methods should be pursued whenever possible. Given the data on efficacy and safety, ovarian tissue cryopreservation should be considered an established fertility preservation technique with limited effectiveness and offered to carefully selected patients.

Ovarian suppression with GnRH analogues

A number of randomized controlled trials (RCTs) and meta-analyses have explored the benefits of GnRH analogs during chemotherapy (51–63). However, the use of GnRH analogues for ovarian protection during alkylating chemotherapy remains controversial. Several RCTs have demonstrated that menstrual function and ovulation are more likely to occur in patients with breast cancer after cotreatment with GnRH agonists during chemotherapy compared with those who did not receive this therapy (59). Benefits in terms of fertility outcomes in this population have been inconsistent, and studies have been limited by inadequate follow-up and few assessments of surrogate measures of fertility, rather than pregnancy rates (55, 57, 64). Although GnRH analogues are not currently approved by Food and Drug Administration (FDA) for fertility preservation, these medications may be used ''off-label.'' Given the evidence of efficacy, GnRH agonists may be offered to patients with breast cancer to reduce the risk of premature ovarian insufficiency and possibly increase the chance of future pregnancies. However, GnRH agonists should not be used in place of other fertility preservation procedures, such as egg or embryo cryopreservation. Further studies are required to establish the efficacy of this treatment and to determine which patients are the best candidates for its use. Nonetheless, this therapy may help to prevent heavy bleeding in patients with thrombocytopenia related to chemotherapy and stem cell transplantation, and it should be considered in such patients (65). Administration of depot GnRH agonists soon after trigger for oocyte retrieval has been associated with OHSS, and therefore, should be delayed for at least 7–14 days after retrieval, but chemotherapy should not be postponed (66).

Ovarian transposition

Patients requiring local pelvic radiation may benefit from transposition of the ovaries to sites away from maximal radiation exposure (67–70). Ovarian transposition may be accomplished at the time of initial oncologic surgery or at a later time. It is important to recognize that this procedure may preclude future transvaginal oocyte retrieval if IVF is required. Transabdominal retrieval may be accomplished in some patients (71). Outcomes on preservation of endocrine and reproductive function with ovarian transposition are age-dependent. A retrospective study of patients undergoing ovarian transposition found that 71.2% of patients aged 30 years or older underwent menopause, whereas only 26% of patients younger than 30 years became menopausal after treatment (72). The location of the transposed ovary is also important to consider; a distance of 4 cm from the field of radiation is recommended (73).

Conservative treatments for reproductive malignancies

Patients undergoing surgery for cervical, endometrial, ovarian cancer, or borderline tumors of the ovary may be candidates for conservative surgical approaches by way of fertility-sparing surgery, oophoropexy, or, in the case of endometrial disease, initial medical therapy. The success depends on the diagnosis and treatment (74–77). If a hysterectomy is performed, these patients should be counseled regarding a gestational carrier.

OTHER/EMERGING FERTILITY PRESERVATION STRATEGIES

In vitro maturation

In vitro maturation (IVM) is an emerging strategy for medically indicated fertility preservation. It generally refers to the collection and maturation of immature oocytes retrieved from small follicles after minimal or no ovarian stimulation (78). After maturation in the laboratory, these oocytes may be cryopreserved or fertilized. Most of the studies evaluating the efficacy of IVM have been conducted in patients with polycystic ovary syndrome to minimize the risk of OHSS. Although randomized studies are limited, literature has demonstrated lower pregnancy and live birth rates with IVM compared with traditional IVF (79, 80). However, IVM has some potential advantages for fertility preservation over traditional ovarian stimulation in patients facing gonadotoxic therapy, because less time is required for stimulation, estrogen levels remain in the physiologic range, and there may be less risk of OHSS. Disadvantages include lower success rates and less access to this option because only a few clinics in the US offer IVM (81). A few live births have been reported (82–84). The IVM performed ex vivo in combination with ovarian tissue cryopreservation is described under the section on ovarian tissue cryopreservation.

Uterine fixation and transposition

Uterine transposition and uterine fixation, or suspension, are emerging methods of preserving fertility and ovarian function for patients undergoing pelvic radiation for nongynecological cancers. The objective is to decrease uterine radiation therapy side effects in the setting of pelvic cancers, such as colon or anal cancer. Uterine fixation may be performed by fixing the uterus to the fascia of the anterior abdominal wall as cranially as possible to remove the uterus from the radiation field or by suspending the bilateral round ligaments to the anterior abdominal wall. Uterine fixation or suspension should be performed in conjunction with ovarian

transposition. Alternatively, uterine transposition is a complex surgical technique where the uterus is detached from the vagina and transposed to the upper abdomen with tubes and ovaries. The cervix may then be sutured to the paracolic gutter in the setting of menstrual suppression with hormonal therapy or to the umbilicus with the creation of a stoma for menstrual bleeding (85).

The largest prospective, multicenter observational study included eight patients undergoing pelvic radiation as part of their cancer treatment and had uterine transposition to the upper abdomen performed before irradiation (86). The uterus was repositioned into the pelvis 2–4 weeks after radiation therapy or at the time of rectosigmoid resection, and there was resumption of normal menses and hormonal levels in six of the patients. Cervical ischemia occurred postoperatively in three patients. Three patients attempted natural conception, and two achieved live births with deliveries at 36 and 38 weeks by cesarean section, without complications.

Children and adolescents

Fertility preservation is possible in children and adolescents. Postpubertal females, including those who are premenarchal, are candidates for ovarian stimulation for mature oocyte cryopreservation. One live birth has been reported in an adolescent patient who cryopreserved oocytes at age 17 (87). Although reports of ovarian stimulation in premenarchal females are scarce, a 7-year-old prepubertal patient with mosaic Turner syndrome cryopreserved six mature oocytes after low-dose COS and hCG trigger (88, 89). Care should be taken to avoid OHSS in children and adolescents, while recognizing that hCG is recommended for triggering oocyte maturation in the setting of an immature hypothalamic-pituitary-ovarian axis.

Ovarian tissue cryopreservation with IVM of tissue-derived oocytes may also be offered to this population. Ovarian tissue cryopreservation is currently the principal method to cryopreserve gametes in prepubertal girls. A live birth has been reported in a female who cryopreserved tissue before menarche (live birth after autograft of ovarian tissue cryopreserved during childhood) (90). Working with these individuals and their parents/guardians requires an approach that is sensitive to various levels of physical and psychological development. Close collaboration among primary physicians, reproductive endocrinologists, mental health professionals, and ethicists is helpful (91).

FERTILITY PRESERVATION METHODS FOR MALES

Ejaculated sperm cryopreservation

For postpubertal males, ejaculated semen cryopreservation is an established technology. The process involves masturbation, which is feasible and successful in the majority of adult males and adolescents (92). Ideally, multiple samples should be obtained for cryopreservation to support options of future intrauterine insemination and/or IVF (93). Sperm collection should be performed before the administration of gonadotoxic therapies such as chemotherapy or radiation therapy, as well as before surgical treatment if possible. Males suspected of having testicular cancer should be offered sperm cryopreservation before orchiectomy (94). Some males with cancer may have underlying impairment in spermatogenesis even before cancer therapy, yielding a limited quantity of sperm per ejaculate (95, 96). Patients should be thoroughly counseled about the quality and quantity of their cryopreservation sample(s) and how they can be used in the future.

Medically-assisted ejaculated semen collection

Some males may have difficulty collecting a semen sample because of psychogenic or organic erectile or ejaculatory dysfunction. Pubertal status, anxiety, fatigue, hypogonadism, pain, and comorbidities, such as diabetes, neurologic problems, and side effects from a variety of medications, like opioids and antidepressants, as well as the underlying disease itself, are contributory factors. Counseling and a comfortable environment to collect may be helpful (97). Use of medical therapy can help. Phosphodiesterase type 5 (PDE-5) inhibitors are oral agents that are classically used to treat erectile dysfunction. These inhibitors have been used with success for men experiencing difficulty providing semen samples (98).

Intracavernosal injections with vasoactive agents (i.e., alprostadil, phentolamine, and/or prostaglandin E1), penile vibratory stimulation, or collection of sperm in men with retrograde ejaculation could still prove to be effective at helping the patient collect a semen sample with masturbation, although these techniques are very rarely implemented in the population of males undergoing fertility preservation.

Surgical sperm retrieval

Surgical sperm retrieval is an alternative strategy for males who cannot ejaculate via the aforementioned techniques, or who have azoospermia or insufficient sperm in the ejaculate to freeze (99). Oncologic testicular sperm extraction (Onco-TESE) is a widely available and effective procedure (100). The testicular tissue containing sperm is processed and cryopreserved shortly after the procedure. The sample can be subsequently thawed, and sperm can be isolated and used for IVF/intracytoplasmic sperm injection at a later time. The Onco-TESE is typically performed in the operating room as an outpatient procedure, and consideration may be given to performing it concurrently with other procedures, such as placement of a central venous access device.

When a patient with a suspected testicular cancer is found to be azoospermic before radical orchiectomy, sperm extraction from the affected testis immediately after orchiectomy on a sterile "back bench" has been successfully utilized; this testicular tissue may represent the only source of viable sperm for cryopreservation in some patients (100, 101).

The Onco-TESE procedure can be performed with the assistance of operating microscope magnification (micro-TESE). This approach can, in some instances, facilitate the identification of more favorable appearing seminiferous tubules (i.e., full, opaque) that are more likely to contain sperm (102, 103).

Electroejaculation

For adults and peripubertal males with psychogenic anejaculation or other severe sexual dysfunction, electroejaculation may be offered as an alternative to Onco-TESE (104, 105). The nonspecific stimulation of pelvic tissues, including the prostate and seminal vesicles via a transrectal probe, may lead to seminal emission (106). Electroejaculation must be conducted under anesthesia, unless the patient also has a complete loss of sensation below the umbilicus (for example, a spinal cord injury).

Posttreatment sperm cryopreservation

Sperm cryopreservation for fertility preservation should be performed before the initiation of cancer therapy (107). The request for cryopreservation of semen samples after cancer treatment has been initiated presents a common dilemma faced by patients and fertility specialists. Chemotherapeutic agents and radiation therapy can cause deleterious genetic changes in sperm that may adversely affect reproductive outcomes and the health of the offspring. For this reason, many centers do not offer sperm cryopreservation after initiation of such cancer therapies. For those centers that do offer this option, patients should be counseled that the cancer therapy could introduce mutations into the sperm that may not be detectable with current or future preimplantation testing techniques (107). Many centers caution that patients use such samples only as a "last resort," in case no other sources of sperm are available.

Prepubertal males

Testicular tissue cryopreservation is an experimental technique performed under institutional review board (IRB)-approved protocols. This approach is offered to prepubertal males who are not yet producing sperm and/or have not yet had seminal emission/ejaculation. If sperm are observed on intraoperative analysis of testis biopsies, those samples can be processed and cryopreserved in the standard fashion used for TESE samples (108, 109). For prepubertal males, testicular tissue cryopreservation is performed with the hope that clinical techniques will emerge that will facilitate the use of immature, prepubertal testicular tissue to facilitate future fertility in affected patients. Current methods under study include in vitro spermatogenesis and germ cell transplantation techniques (110, 111).

Disposition and posthumous assisted reproduction

Clinics should have policies on the disposition of gametes, embryos, and gonadal tissue. They should also have written policies for perimortem and posthumous gamete and gonadal tissue retrieval, including whether the clinic participates in these requests and what documents are required by the individual making requests for tissue cryopreservation (112). Decisions surrounding posthumous reproduction are ethically complex and are addressed in the Ethics Committee opinion (112).

TABLE 2

Potential medical indications for fertility preservation.

Population	Specific conditions, including but not limited to:
Populations at risk because of exposures (treated with surgery, chemotherapy, radiation therapy, hormonal therapies, and other systemic therapies with unknown reproductive effects)	• Cancer patients facing imminent treatment • Survivors of cancer or medical treatments at risk for POI • Hematologic conditions (sickle cell disease, thalassemia) • Rheumatologic conditions • Autoimmune conditions • Gender affirming care (113)
Populations with whom the future risk of pregnancy is too high and will need to use a gestational carrier	• Medically complex conditions • Absence of the uterus related to cancer treatment
Populations with genetic mutations known to impact the health of offspring	• BRCA + for future fertility
Populations with genetic conditions that increase the risk of POI	• Fragile X premutation, other X chromosome abnormalities, including mosaic Turner syndrome • Galactosemia, autoimmune polyendocrinopathy, deficiencies of 17-hydroxylase, aromatase • BPES, Perrault, Fanconi anemia, Werner syndrome, Bloom syndrome, Hutchinson-Gilford progeria, GAPO syndrome • DSD, intersex

BRCA + = BReast CAncer gene positive, BPES = Blepharophimosis, Ptosis, Epicanthus inversus Syndrome, DSD = disorders (or differences) of sex development, GAPO = growth retardation, alopecia, pseudoanodontia, optic atrophy syndrome, POI = primary ovarian insufficiency.

Practice Committee of the American Society for Reproductive Medicine. Medically indicated fertility preservation. Fertil Steril 2026.

Health insurance coverage of medically indicated fertility preservation

Fertility preservation services are medically necessary to decrease iatrogenic infertility (Table 2) (113). Affordability is a key barrier to patients accessing fertility preservation services. All health insurance should cover established fertility preservation services inclusive of long-term storage and subsequent use of cryopreserved materials/tissues as standard of care. Although there is increasing health insurance coverage of medically indicated fertility preservation services, including through laws and employer choice, accessing these benefits through insurance plans may require appeals and independent medical review (114). Health insurance should not use prior authorization to allow for timely delivery of care and set patients' cost-sharing to be at parity

(e.g., copayments, coinsurance, maximum out-of-pocket costs) with other medical services for affordability (115).

SUMMARY

- Systemic therapy, radiation therapy, and surgery for medical conditions in children, adolescents, and adults of reproductive age can harm future fertility.
- Fertility preservation is medically effective in decreasing infertility.
- Established strategies for females include embryo cryopreservation, mature oocyte cryopreservation, ovarian tissue cryopreservation, and conservative management of reproductive malignancies.
- The GnRH agonist suppression (in breast cancer), ovarian transposition, and conservative gynecologic surgery have been shown to preserve ovarian function and may improve fertility.
- Emerging strategies include IVM and uterine fixation/transposition.
- Established strategy for males is sperm cryopreservation, which may require medical or surgical assistance.
- Postpubertal females, including those who are premenarchal, are candidates for ovarian stimulation for mature oocyte or embryo cryopreservation.
- Ovarian tissue cryopreservation is currently the principal method to cryopreserve gametes in prepubertal girls.
- Testicular tissue cryopreservation is currently considered investigational in prepubertal boys.

CONCLUSIONS

- All patients facing treatments that may impair reproductive function and who are at risk of premature gonadal failure deserve prompt counseling regarding their options for fertility preservation and rapid referral to an appropriate program.
- All patients should be counseled on known and unknown reproductive risks of planned medical treatments.
- Clinics offering fertility preservation should have the expertise and infrastructure to provide timely interventions. Programs unable to provide a specific component of fertility preservation services should still counsel patients about available options and/or provide expeditious referrals to programs with the available resources.
- Patients should be offered appropriate fertility preservation options. For patients undergoing COS or sperm banking, multiple collections may be considered to procure sufficient materials to maximize the chance of future pregnancy. After treatment fertility preservation may be considered in females who have been exposed to medical treatments that increase risks of premature ovarian insufficiency or infertility and subsequently have a residual but narrower window of remaining ovarian function, as well as females who underwent fertility preservation but have insufficient cryopreserved materials for a reasonable chance at achieving their goal family size.
- Medical complexity of patients should be considered to minimize risks of fertility preservation procedures.
- Fertility preservation should be offered to children with future fertility potential.
- Fertility preservation services are medically necessary to decrease iatrogenic infertility. All health insurance should cover established fertility preservation services inclusive of long-term storage and subsequent use of cryopreserved materials/tissues as standard of care. Health insurance should not use prior authorization to allow for timely delivery of care and set patients' cost-sharing to be at parity with other medical services for affordability.

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Preservación de Fertilidad en pacientes con indicaciones médicas: opinión del comité.

Preservación de la fertilidad en pacientes con indicaciones médicas: opinión del comité Comité de Práctica de la Sociedad Americana de Medicina Reproductiva, Sociedad Americana de Medicina Reproductiva, Washington, D.C., EE. UU. Los pacientes que van a someterse a terapias que implican un riesgo para su fertilidad o que presentan riesgo de insuficiencia ovárica prematura deben recibir asesoramiento oportuno sobre las opciones disponibles para la preservación de la fertilidad. La preservación de la fertilidad puede ofrecerse mejor mediante programas integrales diseñados y dotados específicamente para afrontar los desafíos únicos que afrontan estos pacientes. Este documento reemplaza al titulado «Preservación de la fertilidad en pacientes sometidos a tratamiento gonadotóxico o gonadectomía: opinión del comité», publicado por última vez en 2019.

Check for updates

Fertility Preservation in People With Cancer: ASCO Guideline Update

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by clinicians and should be used in conjunction with independent professional judgment. Guidance may not be applicable to all patients, interventions, diseases or stages of diseases. Guidance is based on review and analysis of relevant literature, and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in Appendix 1 and 2 (online only) for more.

PURPOSE To provide updated fertility preservation (FP) recommendations for people with cancer.

METHODS A multidisciplinary Expert Panel convened and updated the systematic review.

RESULTS One hundred sixty-six studies comprise the evidence base.

RECOMMENDATIONS People with cancer should be evaluated for and counseled about reproductive risks at diagnosis and during survivorship. Patients interested in or uncertain about FP should be referred to reproductive specialists. FP approaches should be discussed before cancer-directed therapy. Sperm cryopreservation should be offered to males before cancer-directed treatment, with testicular sperm extraction if unable to provide semen samples. Testicular tissue cryopreservation in prepubertal males is experimental and should be offered only in a clinical trial. Males should be advised of potentially higher genetic damage risks in sperm collected soon after cancer-directed therapy initiation and completion. For females, established FP methods should be offered, including embryo, oocyte, and ovarian tissue cryopreservation (OTC), ovarian transposition, and conservative gynecologic surgery. In vitro maturation of oocytes may be offered as an emerging method. Post-treatment FP may be offered to people who did not undergo pretreatment FP or cryopreserve enough oocytes or embryos. Gonadotropin-releasing hormone agonist (GnRHa) should not be used in place of established FP methods but may be offered as an adjunct to females with breast cancer. For patients with oncologic emergencies requiring urgent oncologic therapy, GnRHa may be offered for menstrual suppression. Established FP methods in children who have begun puberty should be offered with patient assent and parent/guardian consent. The only established method for prepubertal females is OTC. Oncology teams should ensure prompt access to a multidisciplinary FP team. Clinicians should advocate for comprehensive FP services coverage and help patients access benefits.

Additional information is available at www.asco.org/survivorship-guidelines.

ACCOMPANYING CONTENT

Listen to the podcast by Dr Harvey, Dr Su, and Dr Loren at https://ascopubs.org/do/fertility-preservation-people-cancer-guideline-update

Appendix

Data Supplement

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TARGET POPULATION AND AUDIENCE

Target Population

People with cancer who are at risk of infertility due to cancer-directed treatment.

Target Audience

Medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, advanced practice professionals, surgeons, nurses, social workers, psychologists, and other members of the clinical care team.

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INTRODUCTION

Fertility preservation (FP) is an essential consideration in the care of children and reproductive-aged people with cancer, particularly as advances in cancer treatments have significantly improved long-term survival rates. Many cancer-directed therapies, including chemotherapy, radiation, and surgery, pose a risk to reproductive health, making it critical to address fertility concerns as early as possible in the treatment planning process and through survivorship.[1] Despite the recognized importance of FP, there remains a need for consistent, current, evidence-based guidance for health care clinicians.[2] Patients often do not receive adequate information or timely referrals to fertility specialists before initiating cancer-directed therapy.[3,4] This gap underscores the need for comprehensive clinical practice guidelines to assist clinicians in discussing fertility risks and preservation options with patients with cancer.

ASCO first published evidence-based clinical practice guidelines on FP in 2006, and published updated guidelines in 2013[5] and 2018.[6] This guideline update provides a comprehensive approach to assessing, discussing, and offering FP options to people with cancer, ensuring that reproductive potential is preserved whenever possible. It is designed to support health care professionals in integrating FP into the broader framework of cancer care. By offering evidence-based recommendations on FP for adults, adolescents, and children with cancer, this update aims to ensure that patients are fully informed of their options and supported in making decisions that align with their long-term reproductive goals.

In this guideline, the terms *male* and *female* are defined based on biological sex, specifically focusing on reproductive anatomy at birth. *Male* refers to individuals born with testes, while *female* refers to those born with ovaries. This binary classification centers on physical attributes typically associated with biological reproduction. From here on, the guideline will refer to individuals as *males* or *females* based on this definition.

GUIDELINE QUESTION

This clinical practice guideline update addresses one overarching clinical question: What are the recommended FP options for people with cancer who are to undergo or have completed cancer-directed treatments?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only).

The recommendations were developed by using a systematic review of evidence published after the previous guideline literature search in 2013. PubMed was searched from January 1, 2013, through November 16, 2023, for systematic reviews, randomized clinical trials (RCTs), and observational studies. The literature search was rerun on September 20, 2024, to identify articles published since November 2023. The reference lists of all identified articles were also hand-searched for additional studies. Articles were selected for inclusion in the systematic review based on the following criteria:

- Population: people who are to undergo or have completed cancer-directed treatments that threaten fertility, including prepubertal patients with cancer.
- Interventions and comparisons: for females, methods of oocyte preservation, embryo cryopreservation, ovarian tissue cryopreservation (OTC), oocyte in vitro maturation (IVM), ovarian tissue transplantation (OTT), ovarian suppression with gonadotropin-releasing hormone analogs or antagonists, ovarian transposition (OT), oophoropexy, trachelectomy, other conservative gynecologic surgery, and stem cell research. For males, methods of sperm cryopreservation, testicular tissue preservation, testicular sperm extraction (TESE), testis xenografting, spermatogonial isolation, and hormonal gonadoprotection.
- Outcomes: maintenance of fertility (live [healthy] birth [gold standard] or surrogate end points), such as ovarian reserve (anti-Müllerian hormone [AMH], antral follicle count, follicle-stimulating hormone [FSH], and estradiol), acute ovarian failure (AOF), premature ovarian insufficiency or premature ovarian failure; pregnancy (eg, hypertensive disease of pregnancy, severe maternal morbidities) and offspring health (eg, preterm birth, small for gestational age); early and late miscarriages; effectiveness of FP services (before and after treatment); treatment toxicity (both antineoplastic and fertility-preserving); education or increased awareness; quality of life; patient and/or family satisfaction.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, and news articles; and (3) published in a non-English language.

Four full-panel meetings were held, and members were asked to provide ongoing input on the updated guideline development protocol, quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel co-chairs and corresponded with the panel via e-mail to coordinate the process to completion. Ratings for the strength of the recommendation and evidence quality are provided with each recommendation, defined in Appendix Table A2. The quality of the evidence was assessed using AMSTAR (Assessment of Multiple Systematic Reviews), the Cochrane Risk of Bias tool, Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I), and elements of the GRADE quality assessment and recommendations development process.[7,8] GRADE quality assessment labels (ie, high, moderate, low, and very low) were assigned by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. All funding for the administration of the project was provided by ASCO.

Guideline Review and Approval

The draft recommendations were released to the public for open comment from September 23, 2024, through October 7, 2024. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with 35 written comments received. A total of 15 respondents either agreed or agreed with slight modifications with 19 of the 26 total recommendations and there was disagreement from one to two respondents with seven of the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

The draft was submitted to three external reviewers with content expertise. It was rated as high quality, and it was agreed it would be useful in practice. Review comments included clarifying that the risk of reimplanting malignant cells in patients with leukemia and measurable residual disease (MRD) at the time of OTC is theoretical, removing language suggesting gonadotropin-releasing hormone agonist (GnRHa) is appropriate as an adjunct to females with breast cancer and stating explicitly that GnRHa should never be used for FP, removing discussions on cervical and endometrial cancers in the children section, and adding a sentence regarding potential legal consequences of creating embryos. These comments were reviewed by the Expert Panel, and any necessary changes were integrated into the manuscript as appropriate. All revisions were resolved through majority consensus. Additionally, a guideline implementability review was conducted. Based on this review, revisions were made to the draft to clarify recommended actions for clinical practice.

All changes were incorporated into the final manuscript prior to ASCO Evidence Based Medicine Committee (EBMC) review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Characteristics of Studies Identified in the Updated Literature Search

A total of 731 studies were identified in the initial updated literature search. The refreshed literature search identified an additional 119 studies. After applying the eligibility criteria, 166 studies remained. Thirteen clinical practice guidelines,[9-21] 65 systematic reviews,[22-40,41-60,61-86] 6 RCTs,[87-93] and 82 observational studies[94-110,111-130,131-150,151-175] form the evidentiary basis for the guideline recommendations.

The identified studies were published between January 2013 and September 2024. A summary of key outcomes and risks for FP options are reported in Tables 1 and 2.

Evidence Quality Assessment

The quality of evidence was assessed for each included study, and factors such as study design, consistency of results, directness of evidence, precision, and magnitude of effect were also assessed by one reviewer. Systematic reviews and meta-analyses were evaluated using the AMSTAR rating.[176] To evaluate RCTs, research design characteristics including random assignment, blinding of outcome assessment(s), selective reporting, complete outcome data, and conflicts of interest were evaluated. The quality of observational studies was informed by the ROBINS-I tool.[177] Each element in the RCT and observational study assessment was rated as having low, uncertain, or high risk of bias. Refer to Appendix Table A2 for definitions for the

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TABLE 1. Key Outcomes and Risks for FP Options for Males

FP Method	Time Commitment and Timing of Procedure	Key Efficacy Outcomes and Findings	Risks, Limitations, and Considerations
Sperm cryopreservation	Repeated visits, multiple samples are recommended, requiring several visits to a clinic; before therapy	Gold standard proven to result in successful pregnancies and live births; widely accepted and practiced	Safe, noninvasive; decreased sperm quality after cryopreservation; requires inseminations or IVF to achieve pregnancy; variable success depending on initial sperm quality and health status; storage costs
TESE and cryopreservation—postpubertal	Surgical procedure; should occur before therapy or >6-12 months after completion of therapy for individuals azoospermic after therapy	Effective alternative method to collect sperm when ejaculation is not possible; capable of resulting in successful pregnancies with IVF	Safe procedure; requires IVF to achieve pregnancy; surgical risks such as infection and bleeding; psychological impact of invasive procedure; storage costs
TTC—prepubertal	Surgical procedure; should occur before therapy	Experimental; currently only option for prepubertal males	Experimental; safe procedure; risk of cancer reseeding unknown; reproductive potential uncertain; uncertain storage costs

Abbreviations: FP, fertility preservation; IVF, in vitro fertilization; TESE, testicular sperm extraction; TTC, testicular tissue cryopreservation.

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quality of the evidence, and the ASCO Methodology Manual for more information.

For systematic reviews and meta-analyses, AMSTAR scores ranged from 5 to 11 out of a possible 11 points (higher scores indicate higher quality; Data Supplement, Table S1). For RCTs, overall risk of bias ranged from low to moderate (Data Supplement, Table S2). The quality of evidence of the observational studies was assessed from low to high (Data Supplement, Table S3).

RECOMMENDATIONS

All recommendations are available in Table 3.

DISCUSSING RISK OF INFERTILITY WITH PATIENT

Literature Review Update and Analysis

Recommendations 1.1-1.3 remain pivotal, are supported by evidence, and are underscored by their importance to individuals with cancer. For adults of reproductive age and children, screening for and addressing infertility concerns early in the treatment process allows healthcare clinicians and patients to explore various options and to mitigate potential distress associated with infertility. FP counseling can reduce long-term regret and dissatisfaction concerning fertility, and is associated with improved quality of life.[65,99] Indeed, offering FP counseling is perceived by individuals with cancer as critical regardless of their reproductive risk profile, age, parity, cancer prognosis, sexual orientation or identity, financial ability, or other characteristics.[65,94,100-102,178] Information that addresses perceived unmet needs specific to infertility risk and FP is most helpful when provided in a standardized and written format.[65]

Recommendation 1.2 underscores the necessity of referring interested and uncertain patients to reproductive specialists for comprehensive infertility risk assessment and FP counseling and services. Collaboration with reproductive specialists ensures that patients receive tailored information about available options. Patients who received FP counseling from reproductive specialists were more likely to pursue FP compared to those who did not.[95,97,98] This highlights the crucial role of reproductive specialists in facilitating informed decision-making and enhancing patient access to FP services.

Recommendations 1.3 and 1.4 stress the importance of initiating discussions about FP early in the treatment trajectory and documenting these conversations in the medical record. FP resources will vary by setting. Clinicians should identify and refer to outside facilities for services that are not available locally. Early discussions enable informed decision-making and allow patients to explore various FP methods without compromising treatment timelines. Moreover, documenting these discussions ensures continuity of care and provides a reference point for future consultations. In order to address changing patient needs and preferences, ongoing communication regarding FP options throughout cancer survivorship is critical.[96]

RISKS OF INFERTILITY FROM CANCER TREATMENT

Literature Review Update and Analysis

For females, evidence from systematic reviews, RCTs, observational studies, and expert opinions indicate that alkylating agents, radiation to ovaries, and hematopoietic cell transplantation significantly increase the risk of infertility, AOF, and premature ovarian insufficiency (POI), with alkylators and radiation exerting these effects in a dose-dependent manner.[23,71,72,76,103,116,179] Combining alkylating agents with pelvic radiation further increases these risks. Platinum exposure also heightens the risk of POI and reduced ovarian reserve.[76,103] Radiation exposure ranging from 20 to 30 Gy or up to 15 Gy total body radiation can impair ovarian function.[180] Notably, doses as high as 6 Gy in adult females, 10 Gy in postpubertal females, and 15 Gy in prepubertal females are linked to significant infertility risk.[72,73,180-182] The

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TABLE 2. Key Outcomes and Risks for FP Options for Females

FP Method	CPR	LBR	Miscarriage Rate	Ovarian Function Preservation Rate	Time Requirements	Key Outcomes and Findings	Risks, Limitations, and Considerations
Embryo cryopreservation	49%	35%-41%	17%-22%	NA	2-3 weeks from initiation of ovarian stimulation until oocyte retrieval	Lower embryo transfer and higher cycle cancellation rates in females with cancer. Letrozole protocols recommended for hormone-sensitive cancer	Requires sperm; postpones beginning cancer treatment (2-6 weeks); potential OHSS risk; ethical and legal issues including concerns regarding the disposition of embryos if the patient does not survive or changes their mind about future use
Oocyte cryopreservation	35%	26%-32%	11%	NA	2-3 weeks from initiation of ovarian stimulation until oocyte retrieval	Lower fertilization rates in females with cancer. Letrozole protocols recommended for hormone-sensitive cancer	Does not need sperm; postpones beginning cancer treatment (2-6 weeks); potential OHSS risk
Ovarian transposition	3%-49%	18%-55%	—	61%-93%	Surgery time, no treatment delay	Successful pregnancies reported in literature	Rare complications such as bowel obstruction, ovarian cyst formation
Uterine transposition	60%[a]	—	—	NA	Surgery time, no treatment delay	Successful pregnancies reported in literature	Cervical ischemia is the most commonly reported complication
Conservative GYN surgery	18%-74%	11%-89%	8%-31%	Variable	Variable	Recurrence rates: 3.1%-15.7%. Lowest pregnancy rates with radical surgery	Safe, dependent on cancer type and stage
Hormonal suppression using GnRHa	—	—	—	Protective effect on ovarian function (relative risk for maintaining ovarian function, 1.60 [95% CI, 1.14 to 2.24]) [83]	Throughout treatment, may be only option when cancer-directed therapy must be offered urgently	Limited evidence for improved fertility (relative risk of experiencing post-treatment pregnancies, 1.83 [95% CI 1.06 to 3.15] in patients with early-stage breast cancer)[58]; may protect ovarian function to preserve normal hormonal milieu; achieves menstrual suppression during therapy	Should not replace proven FP methods; side effects can include menopausal symptoms such as hot flashes, mood swings, and bone thinning
OTC	44%	19%-32%	7.5%-14%	70%-95% ovarian function restored	No delay for cancer management; requires laparoscopic ovarian tissue procurement with later transplantation	Cryopreservation before chemotherapy improves outcomes	The only available option for prepubertal females; no need for hormonal stimulation; commonly orthotopic; potential malignancy reintroduction
IVM	—	Some live births reported in patients with cancer	—	NA	IVM of oocytes from in vivo ovaries—variable, short course or no ovarian stimulation IVM of ovarian tissue oocytes—same as OTC	Less effective than mature oocyte/embryo preservation	Few ART laboratories with expertise in this technique, very few births to estimate likelihood of outcomes

NOTE. The data summarized are from postpubertal people with cancer. Rates are pooled from meta-analyses.
Abbreviations: ART, assisted reproductive technology; CPR, clinical pregnancy rate; FP, fertility preservation; GnRHa, gonadotropic-releasing hormone agonist; GYN, gynecologic; IVM, in vitro maturation; LBR, live birth rate; NA, not applicable; OHSS, ovarian hyperstimulation syndrome; OTC, ovarian tissue cryopreservation.
[a]Rate reported in a review of 18 patients, with three pregnancies out of five that tried.[85]

TABLE 3. Summary of Fertility Preservation Recommendations

Overarching Topic	Recommendation
General Note. The following recommendations (strong or conditional/weak) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.	
Discussing risk of infertility with patient	1.1. Clinicians caring for adult and pediatric patients with cancer should discuss the possibility of infertility as early as possible before treatment starts to preserve the full range of options. (Evidence quality: Moderate; Strength of recommendation: Strong)
	1.2. Clinicians should refer patients who express an interest in fertility preservation, and those who are uncertain, to reproductive specialists. (Evidence quality: Very low; Strength of recommendation: Strong)
	1.3. Clinicians should initiate the discussion regarding infertility with the knowledge that it can ultimately reduce distress and improve quality of life, even if the patient does not undergo fertility preservation. (Evidence quality: Moderate; Strength of recommendation: Strong)
	1.4. Additional discussions and/or referrals may be offered yearly when the patient returns for follow-up after completion of cancer-directed therapy or when treatment plans change or evolve, as well as if pregnancy is being considered. The discussions should be ongoing throughout survivorship and documented in the medical record. (Evidence quality: Low; Strength of recommendation: Strong)
	Qualifying Statement for Recommendations 1.3 and 1.4: It is essential that these discussions take place with all patients, irrespective of their reproductive risk profile, current family size, cancer prognosis, sexual orientation or identity, religious beliefs, financial or insurance resources, access to care, or other potential considerations, including disparities.
Risks of infertility from cancer treatment	2.1. Clinicians should offer an evaluation and counseling regarding the risk of reproductive function impairment and infertility to ensure that all patients are appropriately informed and supported in managing the potential reproductive impacts of their cancer treatment. This assessment should consider specific patient groups known to be at increased risk due to the gonadotoxic nature of the therapies they receive or could receive in the future, and those on longer-term treatments that delay or preclude the ability to conceive. It should also consider those for whom the risk remains uncertain due to the unknown reproductive toxicity of many cancer-directed therapies. The effect of chronologic age should also be taken into account for females due to increased infertility risk with concomitant aging. (Evidence quality: Moderate; Strength of recommendation: Strong)
Fertility preservation in males	3.1. Sperm cryopreservation: Cryopreservation of ejaculated sperm (sperm banking) should be offered prior to initiating cancer-directed therapy. Health care clinicians should discuss sperm banking with all pubertal and postpubertal males prior to receiving cancer treatment. (Evidence quality: High; Strength of recommendation: Strong)
	Qualifying Statement for Recommendation 3.1: More sperm samples will provide greater flexibility in future fertility treatments, ie, inseminations versus IVF. While fertility clinicians empirically recommend a minimum of three ejaculates of sufficient quality, achieving this may not be feasible for all patients. Clinicians should adopt a flexible approach and collect as many ejaculates as possible before the start of gonadotoxic therapy. Importantly, any cryopreserved sperm can offer a chance for biological parenthood.
	3.2. Testicular sperm extraction (TESE): TESE with sperm cryopreservation should be offered to pubertal and post-pubertal males who cannot produce a semen sample, before cancer treatment begins. (Evidence quality: High; Strength of recommendation: Strong)
	3.3. Hormonal gonadoprotection: Hormonal suppression therapy should not be offered to males as an approach for preserving fertility. It is not effective and therefore not recommended. (Evidence quality: High; Strength of recommendation: Strong)
	3.4. Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation in pre-pubertal males and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols. (Evidence quality: Very low; Strength of recommendation: Strong)
	3.5. Post-treatment setting: Males should be advised of a potentially higher risk of genetic damage in sperm collected soon after initiation and completion of antineoplastic and/or radiation therapy. It is strongly recommended that sperm be collected before initiation of treatment because the quality of the sample and sperm DNA integrity may be compromised after a single treatment. Although sperm counts and quality of sperm may be diminished even before initiation of therapy, and even if there may be a need to initiate chemotherapy quickly such that there may be limited time to obtain optimal numbers of ejaculate specimens, these concerns should not dissuade patients from banking sperm. Intracytoplasmic sperm injection allows the future use of a very limited amount of sperm; thus, even in these compromised scenarios, fertility may still be preserved. (Evidence quality: Low; Strength of recommendation: Strong)
Fertility preservation in females	4.1. Embryo cryopreservation: Embryo cryopreservation should be offered as it is an established fertility preservation method, and it has routinely been used for storing embryos after in vitro fertilization. (Evidence quality: High; Strength of recommendation: Strong)
	4.2. Mature oocyte cryopreservation: Cryopreservation of unfertilized oocytes should be offered as it is an established fertility preservation method and may be especially well suited to females who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing. Oocyte cryopreservation should be performed in centers with the necessary expertise. (Evidence quality: High; Strength of recommendation: Strong)
	Qualifying Statements for Recommendations 4.1 and 4.2: Embryo and oocyte cryopreservation are both recommended options for fertility preservation in female patients with cancer undergoing gonadotoxic therapy. The choice between embryo and oocyte cryopreservation should be guided by patient preferences, clinical considerations, and individual circumstances including future flexibility, success rates, and legal considerations. The Expert Panel emphasizes shared decision-making among the primary oncology team, the reproductive endocrinology team, and the patient to determine safety and appropriateness of ovarian stimulation and to tailor protocols. Flexible ovarian stimulation protocols for oocyte collection are available. Timing of this procedure no longer depends on the menstrual cycle in most cases, and stimulation can be initiated with less delay compared with older protocols. Thus, oocyte

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TABLE 3. Summary of Fertility Preservation Recommendations (continued)

Overarching Topic	Recommendation
	harvesting for the purpose of oocyte or embryo cryopreservation is now possible on a cycle day–independent schedule. Of special concern in estrogen-sensitive breast and gynecologic malignancies is the possibility that these fertility preservation interventions (eg, ovarian stimulation regimens that increase estrogen levels) may increase the risk of cancer progression or recurrence. Aromatase inhibitor–based stimulation protocols are now well established and may alleviate these concerns. In particular, there is no increased cancer recurrence risk as a result of aromatase inhibitor–supplemented ovarian stimulation.
	4.3. Post-treatment setting: Embryo and oocyte cryopreservation for fertility preservation may be offered in the post-treatment setting to patients who did not undergo fertility preservation before their cancer treatment but are at risk of primary ovarian insufficiency or infertility. They may also be offered to survivors who previously underwent fertility preservation but may not have enough cryopreserved tissue to meet their desired family size, as well as for those who want or need to delay childbearing and consequently face the risk of age-related fertility decline, which may be accelerated in cancer survivors. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying Statement for Recommendation 4.3: In the post-treatment setting, the efficacy of oocyte retrieval and embryo creation is contingent upon the presence of a viable ovarian reserve, which can be assessed through markers such as anti-Müllerian hormone (AMH) levels and antral follicle count (AFC). It is important to acknowledge that the reproductive potential of gametes may be affected by the proximity to cancer treatment. Due to timelines of oocyte development, there may be no oocyte yield within 3 months of last chemotherapy dose. Patients should be counseled on the unknown reproductive potential and offspring health of gametes obtained proximal to gonadotoxic therapy.
	4.4. In vitro maturation (IVM): IVM of oocytes may be offered as an emerging FP method. (Evidence quality: Low; Strength of recommendation: Conditional)
	Qualifying Statement for Recommendation 4.4: IVM has lower pregnancy and live birth rates compared to IVF in females without cancer. The pregnancy and live birth rates of IVM in cancer survivors is unknown.
	4.5. Ovarian transposition: Ovarian transposition (oophoropexy) may be offered to reproductive-aged patients when pelvic irradiation is required. However, because of radiation scatter, ovaries are not always protected, and patients should be aware that this technique is not always successful. Because of the risk of remigration of the ovaries, this procedure should be performed as close to the time of radiation treatment as possible. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying Statement for Recommendation 4.5: Ovarian transposition is not suitable for patients with a moderate or high risk of ovarian metastasis, or those receiving concomitant gonadotoxic chemotherapy.
	4.6. Uterine transposition: Uterine transposition in reproductive-aged patients remains experimental and should be offered only as part of a clinical trial or approved experimental protocols. (Evidence quality: Low; Strength of recommendation: Conditional)
	4.7. Conservative gynecologic surgery: a. For patients with stage IA2 to IB1 cervical cancer, radical trachelectomy may be offered to preserve fertility if the tumor diameter is <2 cm and invasion depth is <10 mm b. For patients with well-differentiated (grade 1) endometrial tumors with minimal myometrial invasion, as confirmed by magnetic resonance imaging, fertility-sparing surgery may be offered. Hormonal therapy using progestins, either orally or via an intrauterine device, is the primary fertility-preserving option for early-stage endometrial cancer. c. Patients with stage IA grade 1 epithelial ovarian cancer after thorough staging may be offered fertility-sparing surgery. Uterine preservation may be considered in other stages and grades to enable future use of assisted reproductive technologies. d. In other gynecologic malignancies, less radical surgeries may be offered to spare reproductive organs when clinically appropriate. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying Statement for Recommendation 4.7: Each surgical decision should balance optimal oncologic care with the patient's fertility goals, involving a multidisciplinary team for comprehensive treatment planning and follow-up care.
	4.8. Ovarian suppression: Gonadotropin-releasing hormone agonists (GnRHa) should not be used in place of established fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation. GnRHa may be offered as an adjunct to females with breast cancer. Beyond breast cancer, the potential benefits and risks of GnRHa warrant further investigation, and trials are encouraged. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	4.9. Ovarian suppression: For patients with oncologic emergencies requiring urgent chemotherapy, GnRHa may be offered and can provide benefits such as menstrual suppression. (Evidence quality: Low; Strength of recommendation: Conditional)
	4.10. Ovarian tissue cryopreservation and transplantation: Ovarian tissue cryopreservation (OTC) for the purpose of future transplantation may be offered to patients with cancer as an established fertility preservation method. As it does not require ovarian stimulation, it can be performed immediately in those unable to delay chemotherapy. In addition, it does not require sexual maturity and hence may be the only method available in prepubertal patients. This method may also be offered as an emerging method to restore global ovarian function. While this option may be offered as an alternative to embryo or oocyte cryopreservation, it may also serve as an adjunct option. Proceeding with OTC should be guided by patient preferences, clinical considerations, and individual circumstances including future flexibility, success rates, and legal considerations. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying Statement for Recommendation 4.10: Evaluating cancer survivors for residual neoplastic cells before ovarian tissue transplantation is essential to mitigate disease transmission risks and to prioritize patient safety. There is a theoretical risk of reintroducing malignant cells but the clinical significance of this is unknown. To reduce this risk, OTC may be deferred until post-treatment MRD negativity is achieved.
Fertility preservation in children	5.1. Clinicians should offer established methods of fertility preservation (eg, semen or oocyte cryopreservation) in children and adolescents who have initiated puberty, with patient assent and parent or guardian consent. For prepubertal children, the only fertility preservation options are ovarian and testicular cryopreservation, the latter of which is currently investigational. (Evidence quality: Moderate; Strength of recommendation: Strong)

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TABLE 3. Summary of Fertility Preservation Recommendations (continued)

Overarching Topic	Recommendation
Role of clinicians	6.1. All clinicians should be prepared to discuss infertility as a potential risk of therapy. This discussion should take place as soon as possible once a cancer diagnosis is made and can occur simultaneously with staging and the formulation of a treatment plan. There are benefits for patients in discussing fertility information with clinicians at every step of the cancer journey. (Evidence quality: Very low; Strength of recommendation: Strong)
	6.2. All clinicians should encourage patients to participate in registries and clinical studies, as available, to define further the gonadotoxic risks of cancer-directed therapies as well as the safety and efficacy of fertility preservation interventions and strategies. (Good Practice Statement)
	6.3. All clinicians should refer patients who express an interest in fertility, as well as those who are ambivalent or uncertain, to reproductive specialists as soon as possible. (Good Practice Statement)
	6.4. Oncology teams should identify and ensure prompt access to a multidisciplinary fertility preservation team including fertility specialists, trained mental-health professionals for emotional support and guidance on family building decision-making, social workers, financial counseling and insurance navigation, and genetic counselors. Effective, timely, and regular communication among team members is essential to provide coordinated, comprehensive care for patients. (Good Practice Statement)
	6.5. Health insurance benefit mandates and benefits for fertility preservation should specify comprehensive coverage of guideline-based fertility preservation services and long-term storage, parity with other insurance benefits, and elimination of prior authorization. Clinicians should advocate for comprehensive insurance coverage of fertility preservation services for their patients with cancer with legislators, insurance regulators, and health plans, as well as for clinic-based resources to help patients access insurance benefits. (Good Practice Statement)

NOTE. The strength of the recommendation is defined as follows: Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.
Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; FP, fertility preservation; GnRHa, gonadotropin-releasing hormone agonist; IVF, in vitro fertilization; IVM, in vitro maturation; MRD, measurable residual disease; OTC, ovarian tissue cryopreservation; TESE, testicular sperm extraction.

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risk of AOF increases with radiation dose to the least affected ovary, with 2 Gy resulting in a 1%-5% risk and ≥50% risk at 24 Gy for patients age 1-20 years.[73] Higher radiation doses to the uterus (≥12 Gy) are associated with uterine toxicity and restricted fetal growth during pregnancy.[73] Radiation exceeding 30 Gy to the hypothalamus notably increases hypothalamic hypogonadism risk, leading to infertility due to anovulation. Removal of both ovaries and/or uterus results in infertility. Long-term cancer-directed therapies that preclude pregnancy also pose infertility risk due to concomitant decrease in fertility with reproductive aging.[104,105] However, evidence regarding the impact of other chemotherapies, targeted therapies, and immunotherapy on fertility and ovarian function remains limited, highlighting the need for preclinical and prospective clinical studies.[183-185]

For males, cancer treatments impact fertility through mechanisms such as spermatogonial stem cell (SSC) and testicular somatic cell destruction, impaired ejaculatory function, and disruption of the hypothalamic-pituitary-testes axis.[152] Alkylating chemotherapy, platinum agents, radiation to the testes, and hematopoietic cell transplants are particularly harmful to spermatogenesis.[20,23,106-108,154,186] While lower doses of testicular radiation and unilateral orchiectomy have less long-term impact, consensus on risk stratification cut points is lacking.[179] Evidence regarding potential toxic effects on reproduction in males from novel therapies, including immune checkpoint inhibitors, antibody-drug conjugates, small molecules, and monoclonal antibody targeted therapies, is scarce and requires further human study.[185]

The Children's Oncology Group recently reviewed phase III clinical trials to assess the gonadotoxic risks associated with standard chemotherapy regimens.[109,110] These therapies were classified as low, moderate, or high risk, and factors influencing these risk levels included the use of alkylating agents or heavy metals, hematopoietic cell transplant conditioning, and radiation aimed at the hypothalamus or gonadal regions. It has been suggested that cumulative exposure of cyclophosphamide with doses exceeding 4 g/m^2 in males or >8 g/m^2 and 12 g/m^2 in pubertal and prepubertal females, respectively, be classified as high risk.[187]

Clinical Interpretation

Cancer-directed treatments pose differential risks to future fertility. As such, risk stratification should be part of clinical infertility risk counseling and FP decision making. Preclinical and prospective clinical data on reproductive risks of novel cancer-directed treatments are lacking and needed. Ongoing discussions on reproductive health with documentation is warranted not only to address fertility needs post-treatment but also to provide post-treatment FP in some females.

FP IN MALES

Sperm Cryopreservation

Literature Review Update and Analysis

The updated literature search identified one systematic review and meta-analysis[26] and two observational studies,[117,118] not included in the systematic review, that investigated the effectiveness of sperm cryopreservation as a method for preserving fertility in male patients with cancer.

The meta-analysis included 69 nonrandomized studies involving 32,234 adult patients referred for sperm analysis and 23,178 patients who cryopreserved at least one sperm sample. The pregnancy, miscarriage, and delivery rates were 28%, 13%, and 20%, respectively.[26] Ten percent of patients failed to cryopreserve sperm, 23% of cryopreserved sperm samples were eventually disposed of, and 9% of cryopreserved sperm samples were used in assisted reproductive technology (ART). However, subgroup analyses showed improved outcomes in recent studies compared to older studies, with higher pregnancy and delivery rates and a lower failed-to-cryopreserve rate.

An additional cohort study included 329 patients, with semen samples collected before cancer treatments, analyzed, and frozen using rapid freezing.[118] The successful cryopreservation rate was 94.5%. Out of the total patients, 8.4% thawed their semen samples for use in ART. The usage rate and embryo transfer rate were significantly higher among patients with testicular cancer ($P < .05$); however, no significant differences were found in pregnancy and live birth rates (LBRs) between patients with testicular cancer and those with other cancers.

In an additional observational study involving 30 male patients with cancer and 30 control donors age 16-45 years, sperm quality was compared between the groups, before and after antitumor treatment in patients with cancer, and before and after sperm cryopreservation.[117] Compared to those without cancer, sperm quality was lower in patients with cancer before treatment ($P = .01$) and further decreased after treatment ($P = .001$).[117] The sperm concentration and progressive sperm mobility after the sperm cryopreservation were significantly lower than that before cryopreservation in both patients with cancer and control donors ($P = .0001$ for all), but DNA fragments of spermatozoa were not significantly affected by cryopreservation ($P = .829$).[117]

A recent cross-sectional study surveyed members of American Society for Reproductive Medicine (ASRM) FP Interest Group and Society for Male Reproduction and Urology to achieve consensus on semen cryopreservation prior to gonadotoxic treatments.[188] Findings indicated that clinicians typically recommend collecting at least three ejaculates if the total motile count (TMC) is 25M or less, and aliquoting each collection to obtain TMC >5M per sample.

Testicular Sperm Extraction

Literature Review Update and Analysis

The updated literature search identified one systematic review[40] and three additional studies[119-121] not captured in the included systematic review.

A systematic review of 34 articles on oncological testicular sperm extraction (oncoTESE) revealed that testicular sperm freezing was possible for 42.9%-57.7% of patients before gonadotoxic treatment, depending on the type of malignant disease.[40] Pretreatment oncoTESEs were primarily conducted in male patients with a testicular tumor, with a positive TESE result in 57.7% of patients. In men with Hodgkin lymphoma and non-Hodgkin lymphoma, spermatozoa were found in 42.9% and 50.0% of TESEs, respectively. These differences were not statistically significant across the three indications ($P > .05$).[40]

A retrospective study analyzed oncomicrodissection testicular sperm extraction (mTESE) procedures in postpubertal males with testicular tumors and severe oligozoospermia or azoospermia at a single center.[119] Nine patients with germ cell tumors (GCTs) underwent bilateral mTESE during orchiectomy. Sperm retrieval occurred in 33% of patients, with one patient retrieving sperm from the ipsilateral testis, one from the contralateral testis, and one from both testes. No complications were reported, and no postoperative hypogonadism was observed. Out of the three successful sperm retrievals, two patients underwent intracytoplasmic sperm injection (ICSI), resulting in two pregnancies: one healthy live birth and one miscarriage.

A multicenter Australian study assessed the sperm retrieval rates of oncoTESE in males with testicular tumors and severe spermatogenic impairment.[120] Out of 13 patients with a mean age of 34.9 years, sperm was retrieved in six of seven patients with GCTs, with three patients having sperm retrieved from the ipsilateral testis and three patients from the contralateral testis. Sperm retrieval did not negatively impact testosterone levels in patients with GCTs. Overall, cryopreserved sperm was used in two patients, with a median follow-up of 38.7 months, resulting in six pregnancies including five healthy live births and one miscarriage.

Post-Treatment

Studies indicate that in patients with chemotherapy-induced persistent azoospermia, the success rates for surgical sperm retrieval range from 37% to 44% per patient, with LBRs between 40% and 59% per couple.[121,153,156,179] One retrospective analysis of 97 survivors of cancer found a successful retrieval and cryopreservation rate of 50.7% in patients with

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nonobstructive azoospermia and 100% in patients affected by retrograde ejaculation or failure of emission.[156]

Hormonal Gonadoprotection

Literature Review Update and Analysis

Evidence does not support the effectiveness of hormonal suppression for FP in males with cancer. The ASCO Expert Panel does not recommend its use, which is consistent with existing American[17] and international guidance.[12,14]

Other Methods to Preserve Male Fertility

Literature Review Update and Analysis

Evidence identified from the updated systematic review indicates that, although cryopreservation of testicular tissue is currently the only option to preserve fertility for prepubertal males and pubertal patients unable to produce a semen sample, testicular tissue extraction and cryopreservation for FP is considered investigational.[10,12,17,189-191]

Risks to Sperm

Literature Review Update and Analysis

Updated evidence[106,192] confirms that antineoplastic agents and radiation therapy (RT) can cause significant genetic damage in conceptuses, although post-treatment DNA damage is influenced both by the type and intensity of the therapy and by the pathological and clinical stage of the disease.[106] Alkylating agents and radiation can induce a high risk of mutations in spermatozoa produced within 1-2 weeks after initiation of therapy.[192] Topoisomerase II inhibitors, and potentially microtubule inhibitors, pose the greatest risk between weeks 5 and 7 of treatment.[192] Nucleoside analogs, antimetabolites, and bleomycin induce mutagenic effects on spermatozoa during weeks 7-10 of therapy.[192]

Clinical Interpretation

It remains the case that sperm cryopreservation is the most effective method of FP in postpubertal males. Due to the significant concerns around genetic damage to sperm collected after initiation of therapy, it is essential to attempt sperm cryopreservation prior to starting cancer-directed therapy. While three collections may be ideal, many males are unable to provide these optimal collections. For such patients, even one collection is important to obtain if possible. Sperm should be cryopreserved in multiple aliquots, even from a single sample, to facilitate options for multiple cycles of insemination or in vitro fertilization (IVF). Other interventions such as TESE may also be considered. Testicular tissue cryopreservation (TTC) is the only potential option for prepubertal males and is best performed under the auspices of an investigational protocol. There is no role for hormonal suppressive therapies in male patients. Table 1 summarizes FP options in males.

FP IN FEMALES

Controlled Ovarian Stimulation

Several established methods of FP for females involve controlled ovarian stimulation (COS) and oocyte retrieval, including embryo and oocyte cryopreservation. Random start protocols are available and may be particularly important for people with cancer so as not to excessively delay cancer-directed therapy.

Literature Review Update and Analysis

The updated literature search identified 10 studies investigating general and oncological risks of ovarian stimulation.[13,34,48,77,87,88,123,124,158,193]

General risks of ovarian stimulation. A systematic review characterized patients who developed ovarian hyperstimulation syndrome (OHSS) after treatment with long-acting GnRHa following controlled ovarian hyperstimulation (COH) for FP from three studies.[34] Only five patients met the eligibility criteria, ranging in age from 15 to 39 years, the majority of whom were diagnosed with breast cancer, and all patients underwent COH for oocyte cryopreservation with concomitant use of letrozole. All five patients developed OHSS with characteristics such as ascites, moderate hemoconcentration and leukocytosis, hyponatremia, and oliguria, after administration of long-acting GnRHa. The interval between ovulation induction and administration of long-acting GnRHa thereafter ranged from 3 to 5 days. All patients were treated conservatively and recovered without complications.[34]

Large-scale studies have confirmed that the risk of OHSS rises when more than 15 oocytes are retrieved, as evidenced by the Society for Assisted Reproductive Technology registry.[13,124] Conversely, females with benign or malignant conditions undergoing ovarian stimulation for cryopreservation cycles and retrieving an average of 10-12 oocytes have not shown increased risks.[13,123,193] Risk of OHSS can be mitigated by GnRH agonist triggers in lieu of high-dose human chorionic gonadotropin (hCG) triggers.[161,162]

Oncologic risks of ovarian stimulation. Concerns about the safety of conventional protocols due to short-term exposure to high estrogen levels have prompted the creation of protocols designed to minimize estrogen exposure in patients with estrogen receptor (ER)–positive tumors undergoing ovarian stimulation for FP. These alternative protocols include the use of the selective ER modulator tamoxifen or the aromatase inhibitor letrozole. However, their effectiveness has not been compared to standard ovarian stimulation in a RCT.[77] While reducing peak estradiol levels, these alternative protocols did not impact the number of oocytes or embryos retrieved.[87] In a

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randomized trial, patients with ER-positive breast cancer who underwent FP with either oocyte or embryo cryopreservation had similar mature oocyte yields whether randomly assigned to tamoxifen-gonadotropin or letrozole-gonadotropin (12 ± 8.6 *v* 11.6 ± 7.5, *P* = .81 [95% CI of difference, −2.9 to 3.7]).[88] However, as the majority of included studies were retrospective and/or had a median follow-up shorter than 5 years, future prospective studies with longer-term follow-up such as the ongoing Pregnancy and Fertility study will help to strengthen these findings.[158]

A systematic review of 15 studies in 4,643 patients reported the outcomes of patients with breast cancer who underwent COS for FP before starting chemotherapy, and the safety of ART following cancer-directed treatment completion.[48] Females who underwent COS (n = 1,594) had a reduced risk of cancer recurrence (risk ratio [RR], 0.58 [95% CI, 0.46 to 0.73]) and mortality (RR, 0.54 [95% CI, 0.38 to 0.76]) compared to those who did not receive FP at diagnosis (n = 2,386). COS did not negatively impact event-free survival (EFS; hazard ratio [HR], 0.76 [95% CI, 0.55 to 1.06]).[48] Similarly, patients exposed to ART after completion of cancer-directed treatments (n = 123) showed an improved recurrence ratio (RR, 0.34 [95% CI, 0.17 to 0.70]) compared to those who did not undergo ART (n = 540), with no difference in EFS observed (HR, 0.43 [95% CI, 0.17 to 1.11]).[48]

Embryo Cryopreservation

Literature Review Update and Analysis

The updated literature search identified four systematic reviews with or without meta-analyses investigating reproductive and safety outcomes of embryo cryopreservation.[30,33,37,47]

Efficacy

Pregnancy and LBR

A meta-analysis of nine studies on pregnancies resulting from embryo cryopreservation found a pooled pregnancy rate of 49.0%.[47] The corresponding LBR was 35.3%.[47] Another meta-analysis, which included 14 studies with 175 females—mostly with gynecological or hematological cancers—found a pooled LBR of 41% (95% CI, 34% to 48%) following frozen-thawed embryo transfer.[37]

Risks

Miscarriage

The risk of miscarriage following frozen-thawed embryo transfer was assessed in a meta-analysis of 10 studies involving 101 females, with a pooled miscarriage rate of 22% (95% CI, 14% to 30%).[37] Another meta-analysis of six studies found the pooled miscarriage rate of 16.9%, based on the cumulative number of miscarriages per embryo transfer.[47] Additionally, a systematic review reported a miscarriage rate of 20%.[30]

Mature Oocyte Cryopreservation

Literature Review Update and Analysis

The updated literature search identified six systematic reviews ± meta-analyses[30,33,34,37,47,48] investigating oncologic, reproductive, and safety outcomes of cryopreservation of unfertilized oocytes and an additional six studies[88,122,123,126,127,193] focusing on FP in females with hormone-sensitive cancer.

Efficacy

Clinical Pregnancy Rate

Pooled data from seven studies reporting on clinical pregnancies resulting from oocyte cryopreservation found a rate of 34.9%.[47]

LBR After Oocyte Vitrification

The updated evidence of pooled data estimates that LBR after IVF with vitrified oocytes ranges from 26% to 32%.[30,37,47] Embryo cryopreservation is associated with LBRs ranging from 35% to 41%, while oocyte cryopreservation is associated with LBRs ranging from 26% to 32%.[30,37,47]

Risks

Miscarriage

Eight studies involving 177 females were analyzed for miscarriage after IVF with vitrified oocytes.[37] Using a random-effect model, the percentage of females experiencing miscarriage was 11% (95% CI, 6% to 19%). In data pooled from 14 RCTs, the risks of pregnancy loss were not increased with letrozole versus clomiphene (risk difference [RD], −0.01 [95% CI, −0.06 to 0.04]), and the risks were reduced when pooling data from six cohort studies (RD, −0.09 [95% CI, −0.17 to −0.00]).[78]

Potential Risks to Offspring

The long-term follow-up of 15 children conceived with cryopreserved oocytes in 508 patients with cancer between 1996 and 2021 revealed all the children had normal growth and development, although one minor malformation (labiopalatoschisis) was reported.[129] These findings are consistent with older reports of a congenital anomaly incidence of 1.3%.[128] Furthermore, when compared to fresh oocytes, long-term cryopreservation does not appear to result in an increased occurrence of embryonic aneuploidy.[150]

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Post-Treatment Embryo or Oocyte Cryopreservation

While evidence indicates patients in the post-treatment setting are more likely to cancel during stimulation and obtain fewer oocytes and embryos compared to pretreatment or age-matched patients without cancer,[125,131,151,159,163] it is feasible to stimulate multifollicular development, retrieve oocytes, derive embryos, and have live births. On the timing of when it is ideal to undergo post-treatment embryo or oocyte cryopreservation, long-term follow-up of AMH levels, which reflect ovarian reserve, shows that post-treatment AMH levels typically increase for 2-3 years, plateau for 10-15 years, and then decline.[155,179] This trend is consistent for low and moderate gonadotoxic treatments, but for highly gonadotoxic treatments, AMH levels decline sooner after the initial peak, indicating an optimal recovery period for maximizing oocyte yield.[179] AMH trajectories indicate a possible timing window for FP for some but not all survivors.[160]

For females desiring FP soon after start of cancer therapy, successful ovarian stimulation and oocyte retrievals have been reported,[131,151,167,169] but the fertility potential and offspring health risks of oocytes from recently exposed to cancer-directed treatments are unknown.

Clinical Interpretation

Embryo and oocyte cryopreservation are established methods of FP, with the strongest effectiveness data for embryo cryopreservation, although live birth data are ART clinic-dependent. Post-treatment FP is feasible for females at risk of iatrogenic infertility who did not undergo pretreatment FP or who did not cryopreserve enough oocytes or embryos to support their family building goals. As such, the opportunity to undertake these services both before and after cancer-directed treatment to prevent iatrogenic infertility is central to FP care. The decision to freeze oocytes versus embryos should be made by the patient following counseling on differences in effectiveness, their personal wishes and goals, financial costs, and legal landscape.

Ovarian Suppression

Literature Review Update and Analysis

Evidence from existing guidelines,[9,13-15,17] systematic reviews and meta-analyses,[18,34,57,58,60,62,64,70] randomized trials,[90-93] and observational studies[130,132,133] provide the updated evidence base for GnRHa in patients undergoing alkylating chemotherapy.

Efficacy

The evidence does support an increased likelihood of preserved ovarian function and pregnancy among patients with cancer undergoing concurrent GnRHa and alkylating chemotherapy treatment compared to those who do not receive GnRHa.[18,58,62,64,70,90,92,133,194] However, evidence supporting improved fertility outcomes for most types of cancer or in females receiving other systemic cancer-directed treatments remains limited.[57,58,60,62,70,93] A meta-analysis revealed that out of 873 females with early-stage breast cancer treated with GnRHa during chemotherapy in five trials, 37 (10.3%) experienced post-treatment pregnancies, compared to 20 (5.5%) treated with chemotherapy alone, indicating a higher incidence rate ratio of 1.83 (95% CI, 1.06 to 3.15; $P = .03$).[58] Nevertheless, interpretation of the evidence is challenged by the lack of blinding in trials, resulting in a bias evident through increased reported pregnancy attempts in certain trials and a higher incidence of pregnancies among patients in the GnRHa arms.[195] Furthermore, only one trial[93] included post-treatment pregnancy as a preplanned secondary end point.

Clinical Interpretation

GnRHa treatment during systemic cancer-directed treatment modestly increases pregnancies and decreases risks of ovarian insufficiency in breast cancer survivors.[9,58,60-62,70] While applying the findings to other cancers and cancer-directed treatments is controversial, given lack of adequately powered clinical trials, on balance, GnRHa offers menstrual bleeding control and an option for patients who do not have time to undergo oocyte or embryo cryopreservation and are not candidates for OTC. GnRHa does result in estrogen deprivation symptoms, for example, vasomotor symptoms and sexual dysfunction.

In Vitro Maturation

Literature Review Update and Analysis

The updated literature search identified three systematic reviews ± meta-analyses,[43,45,75] one RCT,[89] and 16 observational studies[134-141,144,145,148,164-166,168,170] investigating outcomes of IVM methodologies following oocyte retrieval from in vivo ovaries or from ovarian tissue oocytes. IVM involves culturing immature oocytes to reach metaphase II, a stage in which oocytes can then undergo fertilization.

Efficacy

One systematic review evaluating the benefit of IVM in standard ovarian stimulation among those undergoing FP included eight studies, involving 1,040 patients with cancer, half of whom had breast cancer.[75] A total of 7,711 oocytes retrieved among the cancer population were included in this review. With an overall oocyte maturation rate of 59.7%, IVM led to the cryopreservation of 335 embryos and 2,380 oocytes for future use. Despite variations in patient characteristics, IVM improved the number of mature oocytes following IVF cycles, demonstrating similar survival rates, meiotic resumption rates, and blastocyst formation compared to standard protocols.[75]

The application of IVM among immature oocyte harvest in combination with OTC, ovarian tissue oocyte-in vitro

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maturation (OTO-IVM) was investigated in a systematic review that included 12 studies involving prepubertal and postpubertal females with cancer.[43] The included studies reported a total of 5,724 oocytes retrieved with concurrent OTC. The mean oocyte retrieval was 11.27 oocytes for each patient. Following OTC, 33.8% of immature oocytes successfully matured via IVM and, afterward, 20.4% were successfully cryopreserved.[43] Furthermore, 118 embryos were obtained following IVF or ICSI, with a mean fertilization rate of 64.5% in post-IVM oocytes.[43]

Additional evidence from RCTs and observational studies support both IVM approaches. One study reported high maturation rates, between 57% and 70% for OTO-IVM and between 73% and 82% for immature oocytes retrieved transvaginally (OPU-IVM).[137] This resulted in a mean of 7.6 ± 5.7 oocytes vitrified in OTO-IVM and 4.6 ± 4.9 in OPU-IVM, compared to 6.8 ± 4.6 in ovarian stimulation patients. Moreover, the use of a biphasic IVM system demonstrated higher maturation rates (56% *v* 35%, $P = .0045$), lower degeneration rates after IVM (2% *v* 11%, $P = .2298$), improved fertilization rates (80% *v* 68.4%, $P = .3454$), and higher blastocyst formation rates (16% *v* 0%, $P = .2086$) in patients with gynecological cancer.[144] Another study showed successful oocyte and blastocyst vitrification from oophorectomy samples, especially in younger patients with higher AMH levels.[135] Compared to infertility patients, COS followed by IVM resulted in a lower proportion of immature oocytes (30.0% *v* 43.6%, $P < .05$) and fewer oocytes matured in vitro (1.39 *v* 2.48 per patient, $P < .05$).[148] However, the fertilization and embryo development rates of IVM oocytes were comparable to those of in vivo matured oocytes.[148] Some limitations were identified, such as the presence of ovarian cysts, which could reduce the number of mature oocytes in OTO-IVM procedures. [134] Studies concluded that priming methods (either hCG or GnRHa) before IVM cycles did not significantly affect oocyte maturation, making both methods viable for urgent FP in patients with cancer.[89,136,168]

Several reports of live births following IVM have been documented in the literature, with 16 live births reported among patients with cancer.[137-141,145,164-166,170,196]

Clinical Interpretation

IVM in patients with cancer is an emerging FP method. While obtaining mature oocytes and embryos appears feasible, the processes remain inefficient compared to COS, few ART laboratories have reported expertise in this technique, and there are very few births to estimate likelihood of outcomes reliably.

Ovarian Transposition

Literature Review Update and Analysis

The updated literature search identified four systematic reviews + meta-analyses assessing the efficacy and risks of transposition of the ovaries in patients requiring local pelvic radiation treatment.[31,52,67,79]

Efficacy

Ovarian Function

The efficacy of laparoscopic OT in preserving ovarian function among premenopausal females undergoing pelvic RT for anorectal malignancies was assessed in a recent meta-analysis.[31] A total of 10 studies involving 133 patients with rectal or anal cancer who underwent OT before RT were analyzed and pooled data showed a 66.9% incidence of preserved ovarian function. Another systematic review of OT before radiotherapy analyzed nine studies involving 323 patients.[79] The results showed that both lateral and medial OT effectively preserved endocrine function, with no statistically significant difference between the two groups. Moreover, the only comparative study included in the review[142] found that 76% of patients undergoing OT prior to neoadjuvant therapy had preserved ovarian function at 12 months' follow-up, compared to 0% of patients not undergoing OT ($P < .001$). Among females with cervical cancer who underwent OT, a systematic review of 29 studies involving 1,160 patients showed a high proportion of preserved ovarian function: 91% (95% CI, 83% to 100%) in the surgery alone group, 93% (95% CI, 76% to 113%) in the surgery ± brachytherapy group, and 61% (95% CI, 55% to 69%) in the external-beam pelvic radiotherapy ± brachytherapy ± surgery group.[67] However, a lower rate of ovarian function preservation after OT and pelvic radiotherapy of 61.7% has been reported in pooled data from 1,377 premenopausal females with cervical cancer.[52] This lower rate of ovarian function preservation reported may be attributed to inadequate surgical techniques, which could expose the transposed ovaries to scatter radiation, and advancing patient age, as older patients are more susceptible to ovarian failure even with smaller radiation doses.[197]

Pregnancy

Successful pregnancies following OT have been reported in the literature. Evidence collected in a recent systematic review found six pregnancies in 191 patients (3.14%) with anorectal malignancies.[31] This is in accordance with older studies in other patient populations. A total of 12 live births (one twin) and three miscarriages in 11 patients with Hodgkin's lymphoma over a median period of 14 years after OT have been reported.[147] In 37 patients who underwent OT alongside uterine conservation and pelvic irradiation therapy for pelvic cancer, findings revealed an overall pregnancy rate of 32%, with 12 out of 37 patients conceiving.[146] Among these 12 patients, a total of 18 pregnancies were achieved. Further analysis based on diagnosis categories (group 1: 27 patients with clear cell adenocarcinoma of the vagina and/or cervix; group 2: nine patients with ovarian dysgerminoma and one patient with uterine sarcoma) indicated a lower pregnancy rate in group 1 (15% *v* 80%).[146] Additional

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systematic review evidence indicates that medial OT significantly outperformed lateral OT in terms of reproductive outcomes, with higher pregnancy (49.2% *v* 6.5%, $P = .001$) and LBRs (45% *v* 13.4%, $P = .003$).[79]

Risks

While complications of OT are rare, evidence from systematic reviews ± meta-analyses report on the following:

Surgical Complications

A complication rate of 8.5% from OT has been reported in patients with cervical cancer from systematic review evidence, including small bowel obstruction related to postsurgical adhesions.[52] Data of 30-day postoperative morbidity from seven studies included in a meta-analysis found only one patient (1.2%) encountered a postoperative complication, postoperative aspiration pneumonia, and no intraoperative complications were reported.[31]

Metastases

Among patients with cervical cancer undergoing OT, the incidence of ovarian metastasis is reported to be 0.4%.[52]

Uterine Transposition

Literature Review Update and Analysis

The updated literature search identified two systematic reviews assessing the efficacy of transposition of the uterus in patients requiring pelvic radiation treatment.[24,85]

Efficacy

A systematic review of the literature on uterine transposition as a surgical method to preserve reproductive function in patients undergoing pelvic radiotherapy analyzed 18 reported patients.[85] The median patient age was 29, with rectal cancer being the most common indication. Over a median follow-up of 25 months, three patients achieved successful pregnancies out of five who attempted. One patient experienced tumor recurrence and died.[85]

A second systematic review of uterine displacement techniques compared uterine transposition versus uterine ventrofixation as techniques to preserve uterine function in patients undergoing radiotherapy for rectal or anal cancer.[24] Uterine transposition was found to be more effective in protecting the uterus from radiation doses compared to ventrofixation, with maximum doses of approximately 3.05 Gy and 7.9 Gy for rectal and anal cancers, respectively.[24]

Surgical Risks

Uterine transposition is a complex procedure with higher risks compared to OT, including complications similar to those of a hysterectomy. Uterine ventrofixation is simpler, with no reported complications, and involves lower radiation exposure to the uterus. Despite the promising findings, the limited number of patients and obstetric outcomes prevent definitive conclusions about the preferred technique. Both procedures could be considered for young females with pelvic cancer desiring FP; however, further evaluation and prospective clinical trials are needed to confirm their effectiveness in preserving fertility in patients with cancer.

Conservative Gynecologic Surgery

Literature Review Update and Analysis

The updated literature search identified 24 systematic reviews ± meta-analyses, 16 that focused on patients with cervical cancer,[29,32,35,39,41,42,46,50,51,54,59,63,66,80,143,171] five on ovarian cancer,[27,38,53,68,81] one on early-stage endometrial cancer,[25] and two on gynecologic cancers in general.[49,86]

Efficacy

Reproductive outcomes. A systematic review[49] found reproductive outcomes following fertility-sparing surgery (FSS) varied across tumor types, with pregnancy rates ranging from 45% to 66% in cervical cancer, 74% in ovarian cancer, and 67% in endometrial cancer.

Cervical cancer. In a systematic review of 68 studies encompassing 3,592 patients who underwent FSS for early-stage cervical cancer, the mean clinical pregnancy rate (CPR) was 53.2%.[41] Those who underwent vaginal radical trachelectomy had the highest CPR (67.5%). The mean LBR was 67.8%. Twenty-one percent of pregnancies after FSS required ART.[41] Another systematic review that included 88 studies and 2,838 females with early cervical cancer who underwent FSS found that nearly half attempted pregnancy, with 37.4% achieving at least one pregnancy either spontaneously or through ART.[54] Among these pregnancies, 63.9% resulted in live births, while 37.6% were preterm. The primary cause of preterm births was postoperative cervical length restriction, which lead to cervical incompetence and ascending infections, ultimately increasing the risk of clinical or subclinical chorioamnionitis. Of 64 attempted pregnancies in patients with IB2 cervical cancer and tumors 2-4 cm who underwent neoadjuvant chemotherapy (NACT) and subsequent FSS, there were 76.6% viable deliveries, which included six preterm births (9.4%).[80] Comparing the reproductive outcomes of patients with cervical cancer who underwent minimally invasive surgery (MIS) versus abdominal trachelectomy, pooled data found that among 49 females who attempted to get pregnant, 31.3% (5/16) and 51.5% (17/33) in the MIS and abdominal surgery groups, respectively, succeeded in conceiving.[35] Additional systematic review evidence indicates the lowest pregnancy rate is observed in patients undergoing radical trachelectomy by laparotomy (36%).[42]

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In patients with early-stage cervical cancer ≥2 cm, surgery-based fertility-sparing treatment showed a pregnancy rate of 18%-22%, birth rate of 11%, and preterm rate of 10%.[29,32] Fertility-sparing treatment using the NACT approach showed a pregnancy rate of 44%, with a birth rate of 45% in patients who managed to get pregnant. The preterm rate was 44%, and pregnancy rates and birth rates were statistically significant ($P < .001$).[32]

In 40 patients from 11 studies with cervical cancer and tumor diameter >4 cm who underwent NACT and attempted FP surgery, six patients tried to conceive, and four (67%) achieved at least one pregnancy and three of the five pregnancies (60%) were preterm deliveries (all after radical trachelectomy).[39]

Ovarian cancer. Regarding patients with ovarian cancer, a meta-analysis of 23 studies and 1,126 patients with stage I epithelial ovarian cancer (EOC) after FSS found the pooled pregnancy rate was 30% (95% CI, 0.26 to 0.34), and the pooled natural conception rate was 26% (95% CI, 0.20 to 0.33). The pooled LBR was 27% (95% CI, 0.22 to 0.32).[38]

Endometrial cancer. Pooled data from a recent meta-analysis showed the proportion of females with stage I grade 1 endometrial carcinoma achieving a live birth was 20% (95% CI, 15% to 25%) overall, and 22% (95% CI, 7.0% to 38%) among the patients who underwent hysteroscopic resection plus adjuvant hormonal treatment and achieved complete remission.[25]

Additional evidence for reproductive outcomes in patients with cervical[46,50,51,59,63,66,171] and ovarian[81] cancers is consistent with these findings.

Oncological Outcomes

A systematic review[49] included 153 studies with 7,544, 3,944, and 1,229 patients who underwent FSS for cervical, ovarian, and endometrial cancers, respectively. Overall, recurrence rates after FSS ranged from 3.1% to 4.5% in cervical cancer, 15.7% in ovarian cancer, and 34.7% in patients with endometrial cancer. Rates are comparable to standard surgery for early-stage cervical[143] and ovarian cancers,[27] but higher for endometrial cancer, indicating a heightened need for careful patient selection.[198]

Cervical cancer. For patients with early-stage disease, small tumors, favorable histology, and negative lymph nodes, fertility-sparing options such as cervical conization, simple trachelectomy, and radical trachelectomy may be suitable options. In a systematic review of 68 studies encompassing 3,592 patients who underwent FSS for early-stage cervical cancer, the mean cancer recurrence rate was 3.2%, and the cancer death rate was 0.6% with no statistically significant difference across surgical approaches.[41] Similarly, in 5,862 patients with stage IB1 disease from 275 studies, recurrence rate in patients undergoing simple conization and trachelectomy, and radical trachelectomy by laparoscopic-vaginal approach, laparotomic approach, or laparoscopic approach are, respectively, 4.1%, 4.7%, 2.4%, and 5.2%.[42] In patients having a stage IB2 disease, the recurrence rate after radical trachelectomy by laparotomy was 4.8% ($P = .0035$).[42] Comparing the clinical outcomes of patients with cervical cancer who underwent MIS versus abdominal trachelectomy, pooled data from 1,079 participants found no significant difference in overall survival (OS; HR, 0.51 [95% CI, 0.16 to 1.65]; $P = .881$), recurrence rate (RR, 1.26 [95% CI, 0.68 to 2.33]; $P = .815$), or death rate (RR, 0.54 [95% CI, 0.23 to 1.31]; $P = .680$) between the MIS and abdominal surgery groups.[35] Other meta-analyses[66] also found no difference in OS (odds ratio [OR], 1.56 [95% CI, 0.70 to 3.45]; $P = .27$) or recurrence (OR, 0.63 [95% CI, 0.35 to 1.12]; $P = .12$) between patients with early-stage cervical cancer undergoing open or MIS.

The best approach for managing cervical cancer patients with tumors measuring between 2 and 4 cm, who also want to preserve fertility, remains unclear. Guidelines suggest that a radical trachelectomy combined with pelvic lymph node dissection could be considered as a fertility-preserving option for selected patients.[21] In patients with IB2 cervical cancer and tumors 2-4 cm who underwent NACT and subsequent FSS, a systematic review of 18 studies and 114 patients found the recurrence rate was 6.1% and two patients (1.8%) died of disease.[80] A retrospective study of 733 patients with early-stage cervical cancer who had fertility-sparing procedures found a 7% recurrence rate, with 2.6% of patients dying after a median follow-up of 72 months.[174] Patients with tumors larger than 2 cm had a threefold higher risk of recurrence than those with smaller tumors, irrespective of the treatment radicality.[174]

A total of 40 patients from 11 studies with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix and tumor diameter >4 cm (stage IB3) underwent intravenous NACT and attempted FP surgery.[39] It was successful in 26 patients (65%). A complete pathological response was achieved in 56% of patients, with recurrence occurring in two patients (7.7%). The disease-free and overall survival rates at 4.5 years were 92.3% and 100%, respectively.

Additional evidence for oncologic outcomes in patients with cervical cancer is consistent with these findings.[46,50,51,59,63,171]

Ovarian cancer. A meta-analysis of 23 studies involving 1,126 patients with stage I EOC after FSS found the pooled rate of EOC recurrence was 12% (95% CI, 0.09 to 0.14), which was not significantly different from the rate among patients who underwent radical surgery (OR, 0.77 [95% CI, 0.45 to 1.33]).[38] Similarly, a meta-analysis of eight studies that compared 2,223 patients with stage I EOC undergoing FSS with 5,809 patients undergoing radical surgery found the difference in OS between FSS and radical surgery was nonsignificant (HR, 1.03; [95% CI, 0.80 to 1.31]; $P = .84$).[68] Data on disease-free survival also indicated no difference

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between EOC patients undergoing FSS or radical surgery (HR, 1.07 [95% CI, 0.73 to 1.58]; $P = .72$). A meta-regression of the data indicated there was no statistically significant effect of cancer stage, grade, and histology on the pooled HRs.[68] Evidence from other systematic reviews[27,53,86] support the finding that survival does not seem to be compromised in patients with early-stage EOC, borderline ovarian tumors, or nonepithelial ovarian carcinoma undergoing FSS compared with those undergoing conventional surgery. While current observational studies indicate no significant difference in overall survival or disease-free survival between surgical approaches for patients with stage I EOC, debate remains about the suitability of FSS for patients with stage I EOC who present high-risk features. Additional well-designed studies are required to enhance the evidence quality on this topic.

Endometrial cancer. In patients with stage I grade 1 endometrial carcinoma, evidence from a meta-analysis that included nine studies and 126 patients found medical management with progestins following pathologic diagnosis resulted in an 84% (95% CI, 68% to 100%) complete remission rate. Of those who achieved complete remission, the relapse rate was 9.3% (95% CI, 0.0% to 18%).[25] Additional evidence for oncologic outcomes in patients with endometrial cancer is consistent with these findings,[86] although a pooled relapse rate of 20% with fertility-preserving treatment has recently been reported.[25]

There is emerging evidence on including molecular classification to enhance assessment and treatment strategies for young women seeking fertility-sparing treatment options.[199] However, more research is required before incorporating molecular classification into clinical practice.

OTC and Transplantation

Literature Review Update and Analysis

The updated literature search identified 12 systematic reviews ± meta-analyses[30,36,37,44,47,55,56,69,74,82,84,149] and six additional observational studies[111-114,172,175] investigating reproductive and safety outcomes after OTC and OTT.

Efficacy

Restoration of ovarian function. A systematic review of the literature combined with results from patients in a Danish cohort study found that, out of 237 first OTT patients, renewed ovarian endocrine function was reported in 95% of the females.[149] Further evidence from a systematic review of 25 studies indicates that, in general, 70% of patients that underwent OTT had restored ovarian and endocrine function as well as follicular growth.[55] Return to menstruation was reported to take place between 2 months and 1 year after transplantation.[55] A meta-analysis also considered the restoration rate of ovarian function and included a total of 12 studies involving 499 females.[37] While seven articles reported a 100% restoration rate, analysis of the outcome "no ovarian function restoration" revealed a rate of 6%.[37] Another meta-analysis found menstrual activity outcomes were reported for 273 females assessed in the included trials.[44] Notably, 196 out of these 273 females, constituting 72% of the cohort, were reported to have resumed menstruation. The median time for the return of menstrual activity was found to be 18 weeks, with an interquartile range of 14-22 weeks and a range of 3-48 weeks.[44] A single-center, observational, retrospective, cohort study of females who underwent OTT over a 10-year period found recovery of endocrine function was observed in all but one woman who underwent orthotopic transplantation (92.9%, 13 of 14 patients), in one out of two (50%) females who underwent both orthotopic and heterotopic transplantation, and in all females who underwent heterotopic transplantation (100%, four of four patients).[111] In another observational study of 12 patients who received orthotopic or heterotopic transplants, ovarian endocrine function was restored for all grafts, and time to function and graft longevity were similar between the groups.[172]

Importantly, the return of menstrual activity appeared to align closely with the restoration of hormonal function.[44] Specifically, the median time for FSH levels to decrease to below 25 IU/L was 19 weeks, while the median time for luteinizing hormone levels to drop below 15 IU/L was 19.5 weeks.[44]

Pregnancy after OTC. A recent meta-analysis of 22 studies investigated clinical pregnancies resulting from OTC in females at risk for infertility because of gonadotoxic medical treatment.[47] The CPR, defined as the cumulative number of clinical pregnancies per transplant for ovarian tissue, was pooled and found to be 43.8%. Considering a cohort study included in the meta-analysis that involved 31 patients with cancer, of whom 22 (71%) had received chemotherapy prior to OTC, a 32% pregnancy rate (7/22) was reported for the group with previous chemotherapy exposure compared to no pregnancies (0/9) in those without prior chemotherapy.[173] The cumulative incidence of pregnancy at 3 years was 0% in patients with no prior exposure to chemotherapy and 29% in patients harvested after chemotherapy.[173] However, the pathology differed between the two groups, where 95% of patients undergoing chemotherapy before OTC had hematological malignancies compared to only 11% in those without prior chemotherapy.[173]

LBR after OTC. Examining LBR following IVF after OTC, eight studies involving 266 females were analyzed in a meta-analysis.[37] The resulting LBR stood at 19% (95% CI, 15% to 24%). In another meta-analysis of 20 publications, the LBR for OTC was 32.3%.[47]

Pregnancy after OTT. Evidence from a systematic review of 25 studies indicates that 52% of patients reported pregnancy after OTT, [55] with another systematic review of 20 studies finding 62.5% of females had one or more pregnancies.[56] However, considering evidence from cohort studies only and not case reports, the review found pregnancy rates varied from 3.9% to 19.3% per cycle.[56]

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Pregnancy after OTT was further assessed in a meta-analysis of 18 studies and 547 females.[44] A minimum of one pregnancy was reported in 184 females and, with more than one pregnancy achieved in some females, the resulting overall number of pregnancies reported in the included studies was 290. Similarly, a systematic review found 131 biochemical and clinical pregnancies were obtained in 95 patients.[149] The pregnancy rate for frozen-thawed ovarian tissue transplants was 37% (95% CI, 32% to 43%).[44] Considering the method used to cryopreserve ovarian tissue, pooled data show the cumulative pregnancy rate for ovarian tissue cryopreserved through slow freezing stood at 37%, while for vitrification, it was slightly higher at 44%,[44] although the number of transplants using tissue frozen by vitrification is limited. Among 122 individuals in studies that reported timing of cancer-directed therapy and OTC, 56 patients (46%) had undergone cancer-directed treatment prior to OTC.[44] From these females, a total of 35 pregnancies and 24 live births were reported. Additionally, pooling data from five studies, stratified by whether participants received cancer-directed treatment before cryopreservation, found that participants who did not undergo cancer-directed therapy before cryopreservation exhibited a trend toward higher pregnancy rates, although this did not reach statistical significance.[44] An additional observational study found that, among all OTT females after minimum 1-year follow-up, 10 (38.5%) pregnancies were observed in 26 females, resulting in four live births, two ongoing pregnancies, and four spontaneous abortions.[111]

LBR after OTT. In 1,382 patients from 17 studies analyzed in a recent systematic review, a total of 121 live births (8.8%) occurred from ovarian tissue cryopreserved prior to cancer treatment and reimplanted after patients had completed oncological treatment.[30] Similarly, the live-birth rate for females undergoing ART following OTT was reported to be 10.3% (range, 3.9%-14.0%) per cycle in a systematic review of 20 studies and 40 females.[56] Live births after OTT were further assessed in a meta-analysis incorporating 17 studies and 539 females.[44] Among the females, 134 reported at least one live birth. Since some females experienced multiple live births, a total of 166 live births were reported in the studies included in the meta-analysis. The median number of live births per patient from frozen-thawed transplants was one, with a range of one to 4, while for fresh transplants, the median number of live births per patient was also one, with a range of 1-3. The LBR for frozen transplants stood at 28% (95% CI, 24% to 34%). Spontaneous LBR following OTT was investigated across 11 studies involving 342 females in another meta-analysis and determined to be 33% (95% CI, 25% to 42%).[37]

Risks

Miscarriage. A meta-analysis examining miscarriage following OTT pooled data from 10 studies involving 436 females.[37] The analysis revealed that 14% (95% CI, 9% to 21%) of females experienced miscarriage. Additional evidence from a meta-analysis that pooled data from 13 studies found a miscarriage rate of 7.5% following OTC. [47] Another meta-analysis of 15 studies found the miscarriage rate for frozen transplants was 37% (95% CI, 30% to 46%).[44] Moreover, the pooled evidence from this meta-analysis found that significantly fewer miscarriages occurred with OTC than with embryo cryopreservation.[47] The mean age at cryopreservation in females who had miscarriages was reported to be 27.8 years (standard deviation, 5.8).

Risk of malignancy reintroduction. A systematic review identified existing evidence on minimal infiltrative disease (MID) detection in harvested ovarian tissues.[36] A total of 17 studies were analyzed and it was found that 25 patients tested positive for MID in the OT of at least 115 pediatric patients diagnosed with solid tumors, hematological malignancies, and CNS tumors.[36] Older systematic review evidence from 42 studies and 422 patients found that 7% raised suspicion of malignant cell infiltration.[74] A more recent review identified two reports of cancers occurring within transplanted ovarian grafts.[44] However, a recent case series of six patients with acute leukemia who underwent OTC found no leukemia relapse after transplantation and successful restoration of ovarian function in all patients, with two resulting live births.[175] Screening confirmed no malignant cells in the ovarian tissue before transplantation, and patients remained relapse-free over a median follow-up of 51 months.[175] In patients with leukemia specifically, studies show that chemotherapy before tissue collection, which results in MRD-negative bone marrow, carries a lower risk of malignant cells in the harvested ovarian tissue.[113,114,158]

Risk for offspring. Existing evidence indicates that the health and perinatal outcomes of children born from OTC and OTT, such as birth weight and gestational age, are comparable to those of children from normal pregnancies.[82,112,149] There appears to be no evidence of increased risk of congenital abnormalities or genetic disorders following OTT, with estimated rates at 1.2% being comparable to the 1% to 2% rate seen in the general population.[69] A recent systematic review of 58 studies involving 122 patients and 162 deliveries confirmed that perinatal complication rates after autologous cryopreserved OTT were comparable to the general pregnant population, with a slightly higher incidence of preeclampsia.[82] Most newborns had appropriate birthweights, with low rates of gestational diabetes, preterm premature rupture of membranes, and neonatal anomalies; additionally, lower perinatal complication rates were associated with no prior chemotherapy and natural conception.[82]

Clinical Interpretation

For females with cancer, there are established FP methods (embryo cryopreservation, oocyte cryopreservation, OTC, OT, and conservative gynecologic surgery for early-stage cancers) and emerging ones (IVM, uterine transposition), which vary in effectiveness for future fertility, patient burden, and oncologic risks. In addition, GnRHa for ovarian suppression may be offered as adjunctive therapy for people

with breast cancer, and to people requiring emergent oncologic therapy who are not eligible to receive established methods of FP and/or who may benefit from menstrual suppression, such as those with acute leukemia. It is appropriate to consider postcancer treatment oocyte or embryo cryopreservation for people who did not receive FP prior to cancer-directed therapy or for those who did not preserve enough gametes to meet their family building goals. Cancer-directed treatments can induce not only infertility, but also premature menopause and associated long-term morbidities. Some FP treatments have the potential to preserve ovarian function (GnRHa, OT, ovarian sparing surgery, OTT). Patients may be offered both established and emerging strategies depending on their needs and capability of the reproductive specialist and ART lab. Patients should also be counseled on expectant management, living child-free, and other manners of family building including oocyte and embryo donation, surrogacy, and adoption. Table 2 summarizes FP options in females.

FP IN CHILDREN AND ADOLESCENTS

Literature Review Update and Analysis

The updated literature search identified six guidelines,[9-12,16,19] seven reviews,[23,28,179,200-203] and four additional observational studies[108,113,115,185] investigating FP in children and adolescents who have initiated puberty.

Female Patients

Cancer therapies, such as chemotherapy, radiation, and surgical interventions, significantly impact fertility, especially for gynecologic cancers. Fertility-sparing surgeries such as cervical conization and trachelectomy are options for early-stage cervical cancer, while hormonal therapies for low-grade endometrial cancer may preserve reproductive function. However, more invasive surgeries for advanced ovarian cancers remain controversial due to their impact on fertility and higher risks associated with removing reproductive organs.[11,16]

Oocyte and embryo cryopreservation are the most effective methods for postpubertal females, though they require hormonal stimulation and time, which may not always be feasible before the initiation of cancer treatment. For patients unable to undergo oocyte retrieval, OTC offers an alternative. Originally classified as experimental, OTC has now been endorsed by the ASRM[17] and the American Academy of Pediatrics, [19] among others,[11] as a standard practice.

There are, however, ethical considerations regarding the use of OTC in prepubertal females, especially given the limited evidence of long-term efficacy. Research has shown that ovarian function can return post-transplant, and clinical guidelines now support OTC for this population.[16,202] Furthermore, the risk of reintroducing malignant cells during tissue transplantation is a significant concern, especially for patients with hematologic cancers.[113] Strategies to ensure the safe use of cryopreserved tissues are under development.[16,185]

There are growing concerns about the long-term impact of newer cancer-directed therapies, such as targeted therapies and immunotherapy, on fertility. Studies highlight the importance of incorporating these treatments into fertility discussions as their effects may differ from those of traditional chemotherapy.[16,185] Furthermore, early intervention significantly improves fertility outcomes in female childhood cancer survivors, as noted in a recent systematic review that confirmed positive long-term fertility outcomes for patients undergoing cryopreservation before cancer treatment.[28]

Male Patients

Sperm cryopreservation is the most established and widely accepted method of FP in postpubertal males, with pooled pregnancy rates of 34% with ICSI and 24% per IVF cycle.[26] Sperm can be collected through ejaculation or surgically retrieved when necessary. For males who are unable to produce sperm, surgical sperm extraction followed by cryopreservation provides a backup option.[5,16] However, challenges include minimizing damage during cryopreservation and transplantation, particularly for sensitive testicular tissue.

For prepubertal males, TTC is the only available option. This experimental technique involves the harvesting of SSCs from testicular tissue, with the aim of future fertility restoration. While TTC has not yet been proven to result in human births, animal studies have shown promising results, with successful restoration of spermatogenesis and viable offspring following transplantation.[23,108] Despite being experimental, TTC holds promise, as animal studies have demonstrated the restoration of spermatogenesis and the production of viable offspring following transplantation.[108]

Studies emphasize the risks of alkylating agents on male fertility, particularly in prepubertal males.[108] Research underscores the importance of preserving spermatogonial cells before cancer treatment begins, as these treatments can severely impact spermatogenesis.[108] Research has also found that spermatogonial quantity in prepubertal males undergoing FP is comparable between those with hematological and nonhematological cancers, indicating that TTC can be applied broadly across cancer types.[115]

Clinical Interpretation

The only FP option for prepubertal children is gonadal tissue cryopreservation. For prepubertal females, OTC is now considered an established method of FP but requires an additional surgical intervention and the assent of the child (when possible and appropriate). For prepubertal males, the only option (TTC) remains investigational and should be performed within the context of a clinical trial.

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Ethical and Practical Considerations

FP in children with cancer raises numerous ethical considerations, particularly when balancing immediate life-saving treatments with the potential to preserve future reproductive ability. Ethical dilemmas include obtaining patient assent and parental consent for procedures that may not yield tangible benefits for many years. Children are not typically capable of making fully autonomous decisions regarding their future fertility, so parents or guardians must often decide on their behalf. Furthermore, FP procedures, such as cryopreservation of ovarian or testicular tissue, may carry risks that may delay or complicate cancer treatment, raising questions about whether these risks outweigh the uncertain benefit of preserving fertility for the future. The potential for reintroducing malignant cells during tissue transplantation also remains a concern, although ongoing research is working to mitigate this risk.[202] Long-term fertility management should be a key consideration post-cancer treatment, and ongoing monitoring for fertility-related issues, such as hormonal imbalances, should be part of survivorship care plans.[204,205]

Long-term storage and disposal of reproductive material introduce further ethical complexities, particularly under current and changing US laws. Cryopreserved reproductive tissues may need to be stored for decades, and determining who bears the financial responsibility for this storage can be a significant issue, especially if families face financial difficulties. Additionally, decisions about the disposal of unused or nonviable reproductive material may become complicated if the child reaches adulthood and decides not to use it, becomes incapacitated, or passes away. US laws governing the disposal of reproductive tissue vary by state, and many fertility clinics have agreements in place regarding future use or destruction of stored material.[206] These legal arrangements can sometimes lead to disputes or ethical dilemmas, particularly in cases where a family disagrees about what should be done. This underscores the need for clear, national policies on the long-term storage, disposal, and ownership of reproductive tissues. These policies are needed to ensure individuals with cancer have the information needed to make well-informed decisions on fertility preservation services to support their family building goals.

The use of posthumous reproduction—using stored gametes after a person's death—raises significant ethical and legal questions.[207] Laws governing posthumous reproduction vary widely, and it is important that families understand the legal implications in their jurisdiction. Some fertility clinics may require explicit consent from the patient (or their legal guardians in the case of minors) before allowing gametes to be used for posthumous reproduction, while others might follow default legal frameworks that prohibit such use without clear directives. These variations in clinic policies emphasize the importance of providing comprehensive information to families about the potential future use of stored gametes, ensuring they are aware of the legal and ethical landscape that may impact decisions years later.

ROLE OF HEALTH CARE CLINICIANS

Literature Review Update and Analysis

As with other potential complications of cancer treatment, all clinicians have a responsibility to inform patients about the known and unknown risks that their cancer treatment poses on future fertility. Clinicians should be aware of increasing mandated insurance coverage of medically indicated FP, which varies by state and insurance type, and philanthropic resources, in order to support their patients' access to FP services and reduce medical financial hardship. An algorithm for triaging FP referrals is presented in Figure 1.

Current guidelines continue to underscore the importance of timely referrals to reproductive specialists and psychosocial professionals for patients with cancer at risk of infertility.[9-12,14,15] Referrals should be made as soon as possible. Psychosocial providers, including social workers and psychologists, play a critical role in supporting patients emotionally as they navigate the distress of potential infertility, particularly among patients with cancer who face increased psychological burdens.[22] Studies show that addressing fertility concerns early helps reduce long-term emotional distress. Infertility remains a significant source of distress for cancer survivors, and many express regret when they are not adequately informed of their options.[208]

For people with cancer who are unable to pursue biological parenthood post-treatment, other family-building options like gestational carriers, oocyte, sperm, and embryo donation, and adoption are available. Psychosocial providers can assist patients and families in the decision-making process about FP and disposition of stored gamete options that are legally, morally, and ethically acceptable to them.[209]

LIMITATIONS OF THE RESEARCH AND FUTURE RESEARCH

Review of the literature reveals a paucity of large and/or randomized studies on the effectiveness of FP services. Most data come from cohort studies, case series, small non-RCTs, or case reports. Small sample sizes may have led to underestimation of outcomes such as LBRs, and data on unassisted pregnancies were often missing. Additionally, there is insufficient outcome information on patients who did not return to use their preserved gametes. The lack of detailed reporting on sperm quality creates further uncertainty in assessing the impact of FP on reproductive outcomes. People with cancer infrequently receive FP, which limits our knowledge about the benefits and risks of different interventions, both physically and psychosocially.

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Multilevel barriers exist to the delivery of guideline-concordant FP care, but there are few evidence-based, scalable interventions to support screening patients for FP needs, referring them to reproductive specialists, and facilitating access to affordable FP services to deliver care equitably. Health policies such as insurance mandates for FP are increasing but there are few data on their effectiveness in utilization, affordability, and decreasing disparities, and these mandates often only apply to private insurers. The association between many emerging social determinants of

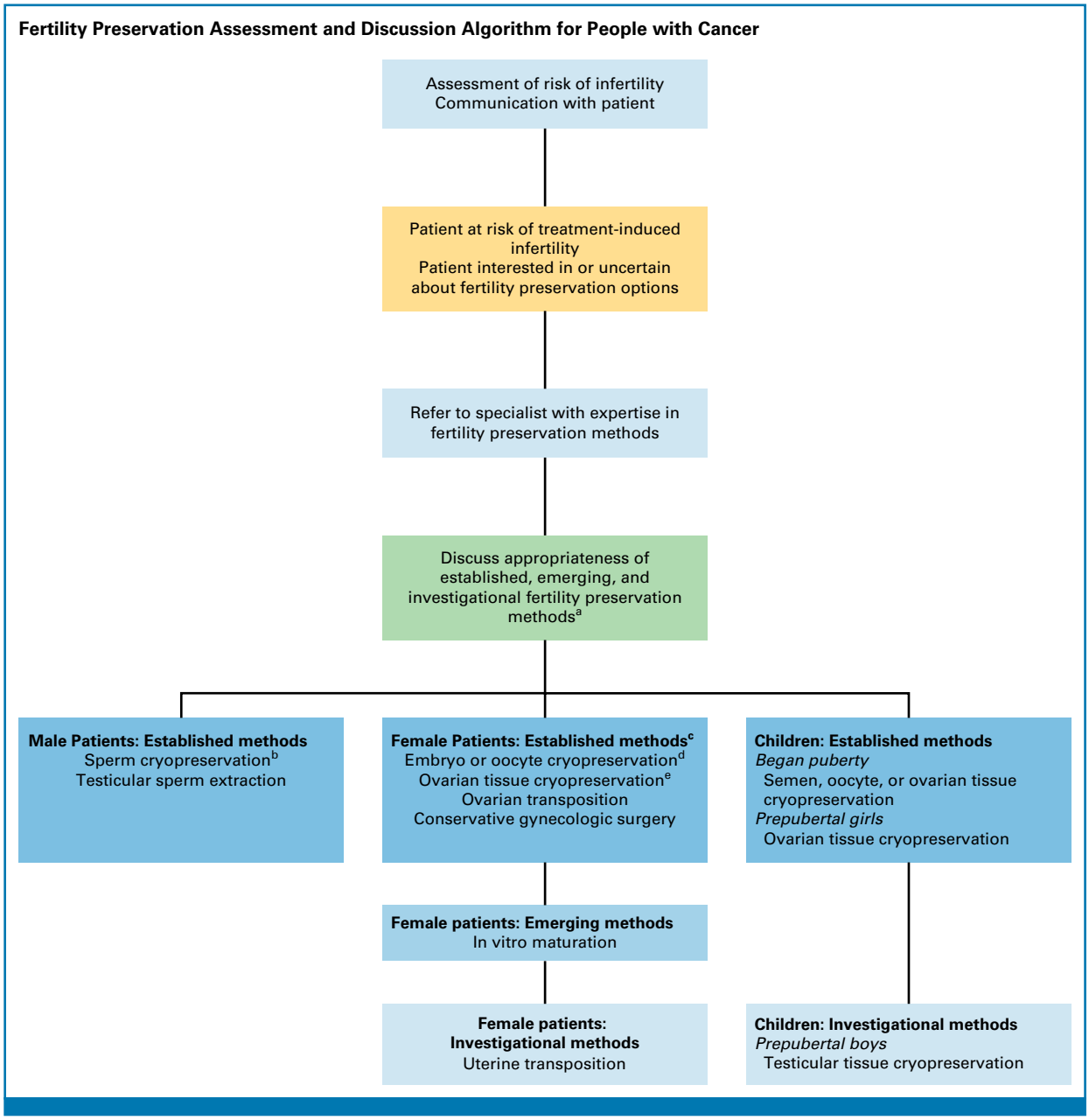


FIG 1. FP assessment and discussion. This is a tool based on an ASCO Guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool are voluntary. www.asco.org/survivorship-guidelines. [a]Patients and fertility clinics should investigate whether the patient's plan covers FP services and where they can receive in-network services. [b]Some patients may proceed with this without the prior step of seeing a reproductive specialist. However, consultation with reproductive specialist is recommended. [c]GnRHa may be offered as an adjunct in females with breast cancer or for patients with oncologic emergencies requiring urgent chemotherapy. [d]May also be offered in the post-treatment setting. [e]Evaluating cancer survivors for residual neoplastic cells before ovarian tissue transplantation is essential to mitigate disease transmission risks and to prioritize patient safety. FP, fertility preservation. ©American Society of Clinical Oncology 2025. All rights reserved. For licensing opportunities, contact licensing@asco.org.

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health and receipt of FP care is understudied. There is also a lack of knowledge on effective implementation of FP care in lower-resource settings. Further research is needed on decision-making regarding the future use of cryopreserved tissue and posthumous reproduction. Additionally, studies should explore approaches to FP in patients with limited life expectancy, including those with metastatic disease. The Expert Panel encourages additional well-designed studies evaluating FP procedures and FP care delivery in people with cancer to help answer these questions. However, the Panel also acknowledges that the traditional gold standard of randomized, controlled, and blinded therapeutic studies may not be feasible in this topic area.

The future of FP procedures for patients with cancer is evolving with innovative techniques beyond current established methods. In females, emerging approaches include the development of artificial ovaries and stem cell–derived neofolliculogenesis, which may offer new hope for improving FP outcomes.[210] Other research is focusing on adjuvant fertoprotective agents aimed at preventing follicle loss after chemotherapy-induced damage.[211] In young male cancer survivors, experimental strategies like SSC transplantation may also hold promise for future FP.[26] Further research and ethical considerations need to be established before the potential and clinical application of these methods is confirmed.

PATIENT AND CLINICIAN COMMUNICATION

Health care clinicians can use the following points for a discussion of infertility and FP with a patient (or parent[s] or guardian[s]):

Inform Patients and/or Families of Individual Risk:

- Some cancer treatments can cause infertility or POI, or for males, oligospermia or azoospermia
- In order to determine an individual's risk, the care team considered a number of factors such as the person's cancer type, age, and treatment plan.
- Based on that information, the care team believe that the person's infertility risk is (high, medium, low, nonexistent, or uncertain).
- The patient's reproductive potential before cancer may also play a role in patient's individual risk (discuss if relevant).

Discuss Common Concerns:

Options

- There may be several options for FP before and after cancer treatment to support family-building goals.
  - For males, the most common and successful option is to collect sperm for sperm banking before the start of treatment. Other experimental options may exist, if sperm banking is not an option.
  - For females, the most established options are embryo and egg freezing, and in some situations, freezing ovarian tissue, moving ovaries away from radiation fields, and conservative surgery of reproductive organs. Other options may exist, if these are not viable options.
- A referral can be made to an appropriate reproductive specialist for a consultation.

Time

- Time is of the essence. Ideally, FP treatments need to be completed before the start of chemotherapy and/or radiation. In some patients, FP treatments post-treatment may be indicated.
  - For males, sperm banking can be done quickly. A collection can be done once every 24 hours to collect the desired number of samples.
  - For females, FP may take 2-3 weeks for established techniques that involve collection of eggs (either egg or embryo freezing). However, some other approaches, including some emerging ones, can implemented sooner, so timely referral to a reproductive specialist is important.

Costs

- There is increasing recognition that FP is an integral part of cancer care and should be covered by insurance. Some employers choose to include FP benefits in their insurance plan. Also, some states require coverage for medically indicated FP for some insurance plans. The levels of coverage vary. The fertility center or sperm bank will be able to check your benefits for you. A patient guide to using insurance for FP, prepared by the University of California San Diego and Alliance for Fertility Preservation, may be useful and can be found online.[212]
- Learn health insurance basics
- Verify FP benefit coverage with health insurance plan
- Confirm FP state-level benefit mandate requirements
- Learn about the appeals process for denials of FP benefit coverage
- Advocacy organizations such as LIVESTRONG Fertile Hope and some pharmaceutical companies may also provide cost-saving programs.

Risks of Pregnancy and Children After Cancer

- Many people worry about the safety of pregnancy after cancer. Data are very limited, but there appears to be no increased risk of cancer recurrence from FP methods or pregnancy, even in hormonally sensitive tumors.
- Similarly, many people worry about the risk of passing cancer along to their children. Aside from hereditary genetic syndromes and in utero exposure to some chemotherapy treatments, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increase the risk of cancer or congenital abnormalities in the progeny.

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Refer to Appropriate Specialists:

Reproductive Specialists

- For more information about FP, a referral can be provided to a local fertility specialist and/or sperm bank.

Mental Health Professionals

- Many people find cancer treatment–related infertility distressing. There is a lot to think about in addition to cancer. Referral to a counselor can be made, if that would be helpful. Many reproductive centers also have counselors available to discuss these issues.

Advocacy Organizations

- Many advocacy organizations such as Alliance for FP and LIVESTRONG Fertile Hope and the Oncofertility Consortium also provide useful information and resources to help facilitate decision-making. They may also have financial assistance programs specifically designed to help with FP.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[213]

HEALTH EQUITY CONSIDERATIONS

Social determinants of health, defined by the World Health Organization as the conditions in which an individual is born, grows, lives, works, and ages, can undermine ASCO's expert recommendations on best practices for prevention, screening, palliative and supportive care, and disease management for many patients with cancer.[214,215] It is important to acknowledge that many people in the United States and elsewhere do not receive the highest level of cancer care due to the long-term impact of structural racism and the consequential unequal distribution of wealth among racial groups.[216] In addition, sexual and gender minority populations experience unique challenges at each stage of the cancer continuum, may face greater risk of developing cancer, and may be diagnosed with cancer at a younger age and a later stage than their heterosexual/cisgender counterparts.[217]

Studies highlight significant disparities in the use of FP, shaped by sociodemographic factors, health care access, and clinician practices. The studies primarily examine traditional determinants—racial and/or ethnic disparities among adults in the United States. There are fewer data on nonheterosexual/cisgender populations and other minoritized populations. Studies have reported that only up to 4% of women with cancer engaged in FP, with lower usage associated with being older at diagnosis, non-Hispanic Black, parous, or residing in nonurban or lower socioeconomic areas.[100,178] Participants in minoritized groups also reported unclear communication and prohibitive costs. [94] Moreover, females with lower education levels, older age, and those with less common cancers are less likely to be counseled.[100,218] Clinician-related factors, such as not initiating fertility discussions or lacking knowledge of FP referral processes, contribute to these disparities.

In the United States, many patients remain unable to reap the benefits of innovative prevention and early detection programs, biomarker testing, and new cancer therapies due to structural barriers including lack of transportation, stable housing, adequate insurance coverage, food insecurity, health literacy, proximity to a dedicated cancer center, and cost of treatment and other services.[219] Additionally, sexual and gender minority populations experience stigma along with barriers to cancer screening, prevention, and treatment that contribute to these cancer disparities.[220] Disparities widen in those who are also from a racial or ethnic minority, underscoring the influence of intersectionality in cancer health disparities.[221]

Further, geographic disparities can also impact the quality of care patients receive. Rural patients are more likely to have worse survivorship outcomes and experience higher mortality rates compared to nonrural patients. This can be attributed, in part, to a lower density of specialists and dedicated cancer centers, as only 21% of nonmetropolitan counties in the United States have one or more practicing oncologists.[222]

Reproductive care should be part of the standard care of all oncology patients. Cost, access, and time for proven FP methods may prevent patients from receiving optimal reproductive care.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of costs through deductibles and coinsurance.[223,224] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended treatments.[225,226] Utilization of FP treatments is associated with medical financial hardship.[227]

Most patients in the United States have insurance coverage through employer-sponsored insurance, Health Insurance Marketplace (Affordable Care Act) plans, Medicaid, military insurance (Tricare, Veterans Administration), or the Federal Employee Health Benefits Program. FP coverage varies among these insurance types. In 2024, 17 states and the District of Columbia passed state-level benefit mandates that require some state-regulated health insurance plans to cover medically indicated FP.[228] The types of included plans vary by US states with these mandates. For example, the Illinois mandate applies to both commercial and Medicaid plans, while the California mandate excludes Medicaid plans. Importantly, only fully funded commercial plans are subject to state mandates, while self-funded plans (typically by large employers) are subject only to federal mandates, which currently do not exist. Moreover, how much cost-sharing is passed to the patient varies by benefit design.

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Discussion of cost can be an important part of shared decision-making.[229] Clinicians should learn about their state's law on FP insurance coverage to know which types of insurance could cover FP services and support patient access of covered services.

When discussing financial issues and concerns, patients should be made aware of any insurance navigation and financial counseling services available to address this complex and heterogeneous landscape.[229]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a community oncologist member on the panel. The additional role of this community oncologist member on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/survivorship-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit www.asco.org/survivorship-guidelines. The Data Supplement for this guideline includes quality assessments, literature search strategy, and PRISMA diagram. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

RELATED ASCO GUIDELINES

- Patient-Clinician Communication[213] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Assessment of Adult Women With Ovarian Masses and Treatment of Epithelial Ovarian Cancer: ASCO Resource-Stratified Guideline[230] (https://ascopubs.org/doi/10.1200/GO.21.00085)
- Management and Care of Women with Invasive Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline[231] (https://ascopubs.org/doi/10.1200/JGO.2016.003954)
- Interventions to Address Sexual Problems in People with Cancer[232] (https://ascopubs.org/doi/10.1200/JCO.2017.75.8995)
- Management of Anxiety and Depression in Adult Survivors of Cancer[233] (https://ascopubs.org/doi/10.1200/JCO.23.00293)
- Survivorship Care for People Affected by Advanced or Metastatic Cancer: MASCC-ASCO Standards and Practice Recommendations[234] (https://ascopubs.org/doi/10.1200/OP.23.00716)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[235] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[236-239] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies describing participants as females with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline Update provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.org, is available at www.asco.org/survivorship-guidelines.

EQUAL CONTRIBUTION

H.I.S. and A.W.L. were Expert Panel Co-Chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Conception and design: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Fertility Preservation in People With Cancer: ASCO Guideline Update

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

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TABLE A1. Fertility Preservation in People With Cancer Guideline Update Expert Panel Membership

Name	Institution	Area of Expertise
H. Irene Su, MD MSCE, Co-Chair	University of California, San Diego, San Diego, CA	Reproductive Endocrinology, Obstetrics Gynecology, Reproductive Sciences
Alison W. Loren, MD MSCE, Co-Chair	Perelman School of Medicine, University of Pennsylvania Philadelphia, PA	Fertility Preservation, Hematological and Medical Oncology
Joseph Letourneau, MD	University of Utah, Salt Lake City, UT	Reproductive Endocrinology
Ann Partridge, MD, MPH	Dana Farber Cancer Institute Boston, MA	Fertility Preservation, Medical Oncology
Rubina Qamar, MD	Aurora Cancer Care, Milwaukee, WI	Community Oncology
Gwendolyn P. Quinn, PhD	New York University Grossman School of Medicine, New York, NY	Medical Ethics, Psycho-Social Oncology
Joyce Reinecke, JD	Alliance for Fertility Preservation, Lafayette, CA	Patient Advocate
James F. Smith, MD	University of California, San Francisco, San Francisco, CA	Urology, Male Reproductive Health
Megan Tesch, MD	Dana-Farber Cancer Institute, Boston, MA	Breast Medical Oncology, Trainee and Early Career Council
W. Hamish Wallace, MD, FRCPCH	Royal Hospital for Children & Young People & University of Edinburgh, Edinburgh, Scotland, UK	Pediatric Cancer Survivorship
Erica T. Wang, MD	Cedars-Sinai Medical Center, Los Angeles, CA	Obstetrics Gynecology, Reproductive Endocrinology
Christina Lacchetti, MHSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

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TABLE A2. Recommendation Rating Definitions

Term	Definition
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects
	In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects
	All or almost all informed people would make the recommended choice for or against an intervention
Conditional/weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists
	In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists
	Most informed people would choose the recommended course of action, but a substantial number would not

NOTE. GRADE Handbook, Schünemann et al.[240]
Abbreviation: FP, fertility preservation.

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In vitro maturation: a committee opinion

Practice Committees of the American Society for Reproductive Medicine, the Society of Reproductive Biologists and Technologists, and the Society for Assisted Reproductive Technology

American Society for Reproductive Medicine, Birmingham, Alabama

The results of in vitro maturation (IVM) investigations suggest the potential for wider clinical application. This document discusses the efficacy of IVM as reported in the published literature to date. This document replaces the document of the same name, last published in 2013. (Fertil Steril® 2021;115:298-304. ©2020 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

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In vitro fertilization (IVF) typically involves ovarian stimulation with the use of exogenous gonadotropins to induce the maturation of gonadotropin-sensitive follicles and inhibit the atresia of nondominant follicles (1, 2). The classic use of the term in vitro maturation (IVM) refers to the maturation of immature cumulus-oocyte complexes (COCs) in culture from prophase I (i.e., from the germinal vesicle [GV] stage) through meiosis I to reach metaphase II (MII) after their recovery from follicles that have not been exposed to the preovulatory trigger (3). This was defined largely in nonhuman animal studies. In clinical human IVF, however, the term IVM is often used to refer to in vitro maturation of oocytes retrieved at the GV or metaphase I (MI) stage from follicles after exposure to exogenous FSH and/or hCG ("follicle priming") to increase the likelihood of obtaining some mature oocytes (4, 5). Interpretation of studies reported in the literature could be clarified if specific terminology was used to delineate between IVM with and without short gonadotropin stimulation, and with and without hCG exposure before retrieval (6, 7). Table 1 provides some definitions of IVM currently in use.

The human oocyte reaches its full size (~100–120 μm in diameter) at the small antral stage, during which time the follicular diameter is only a fraction of its final ovulatory diameter. The ability of an oocyte to resume and complete meiosis is closely linked to follicular diameter (12–15). In humans, the kinetics of oocyte maturation have been studied with the use of oocytes obtained from oophorectomy specimens from nonmalignant gynecologic disorders and then cultured to undergo IVM, reaching MII after 36–48 hours (3).

It should be noted that even if an immature oocyte progresses to the MII stage with the use of IVM (i.e., completes nuclear maturation), it may not necessarily have undergone cytoplasmic maturation and achieved full developmental competence. For a mature oocyte to undergo successful fertilization and subsequent development, synchronization of nuclear and cytoplasmic maturation must occur (16). Nuclear maturation consists of GV breakdown induced by the LH surge followed by resumption of meiosis and extrusion of the first polar body (MII) (3). Cytoplasmic maturation refers to an accumulation of factors that prepare the cytoplasm for fertilization and embryonic development (17, 18). Epigenetic processes are a component of nuclear and cytoplasmic oocyte maturation, influencing development after fertilization (19, 20). For this reason, the potential for epigenetic disruption, such as abnormal methylation of maternally expressed genes, warrants careful evaluation in oocytes matured in vitro (21).

POTENTIAL APPLICATIONS OF IVM

The clinical application of IVM may be limited by alternative evidence-based strategies to successfully mitigate the risk of ovarian hyperstimulation syndrome (OHSS) in high-risk populations. Historically, candidates for IVM have included those at risk for OHSS, including women with polycystic ovary syndrome (PCOS) or polycystic ovary (PCO)–like ovaries and women with estrogen-sensitive cancers. Because significantly less medication is used for stimulation with the use of IVM, and the stimulation is of shorter duration requiring fewer injections and less monitoring, the financial and emotional burden is reduced compared with traditional IVF cycles. In addition, patients with limited time before potentially gonadotoxic cancer treatments may be candidates to use IVM for fertility preservation (22, 23). Finally,

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TABLE 1

Definitions of IVM.

Term in literature	Oocyte maturation	Exposure to hormones	Reference
Biological definition of IVM	GV to MII	No exposure to hCG or LH	Edwards 1965 (3)
Variations on definition of IVM			
Truncated IVF without FSH	GV or MI to MII	hCG primes intermediate follicles, no FSH	Chian 1999 (8)
Follicle priming with FSH	GV or MI to MII	Minimal FSH stimulation, no HCG	Wynn 1998 (9)
Mild-stimulation IVF/ truncated IVF	GV or MI to MII	Minimal FSH stimulation and early hCG administration to prime intermediate follicles	Fadini 2009 (10)
Rescue IVM	Any immature oocytes at retrieval to MII	Controlled ovarian hyperstimulation cycle resulting in GV or MI oocytes denuded of cumulus cells	Sacha 2018 (11)

Note: GV = germinal vesicle; IVF = in vitro fertilization; IVM = in vitro maturation; MI = metaphase I; MII = metaphase II.

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a study has shown the effectiveness of IVM in patients with repeated assisted reproduction failure due to resistant ovary syndrome (24).

IVM IN CLINICAL PRACTICE

Follicular Priming

There have been several clinical studies comparing IVM with conventional IVF using in vitro matured human oocytes in PCO-like and PCOS patients (25–29) and in ovulatory women (26, 30, 31). Several trials have also evaluated the utility of follicular priming versus the retrieval of oocytes from unstimulated antral follicles (10, 25). Three methods of follicular priming have been reported. One method is to minimally stimulate ovaries with low doses of FSH for 3–6 days, followed by retrieval on cycle day 7–10 in the absence of hCG administration. Other approaches use only hCG (single 10,000 IU injection) to "prime" intermediate-sized follicles 36 hours before oocyte retrieval, as well as the addition of minimal FSH stimulation before this hCG priming. This form of priming with hCG is physiologically different than late follicular administration of hCG in a traditional IVF cycle.

Priming with FSH and a single priming injection of hCG on cycle day 6, followed by IVM, in 921 PCOS women resulted in a cumulative live birth rate per cycle of 33.7% (32). A retrospective cohort study comparing IVM with the use of FSH and an hCG priming injection versus conventional IVF in 919 women with high antral follicle count (AFC) reported that although the number of mature oocytes and good-quality embryos was lower in the IVM group, the cumulative live birth rate after one cycle of IVM was 239/608 (39.3%) versus 155/311 (49.8%) for IVF (29).

The combination of gonadotropin and hCG priming compared with single-agent follicular priming has been studied with disparate results. A large randomized trial in 400 women with normal ovaries showed that when both FSH and hCG were used for priming, the percentage of oocytes that matured in vitro and the total number of available mature oocytes was improved, although 20% of recovered oocytes were matured in vivo in this treatment group. Clinical pregnancy rates after fresh embryo transfer were highest when both FSH and hCG were used, 26.5%, compared with 11.8%, 5.4%, and 13.7% in the nonprimed, hCG-primed, and FSH-primed groups, respectively (10). However, embryos in this group likely arose from a combination of both in vivo and in vitro matured oocytes, complicating interpretation of these results.

In several studies from Belgium in which IVM was conducted after a short (3-day) FSH stimulation with no hCG, clinical pregnancy rates have been reported. In a small study of 39 PCO/PCOS patients and 73 IVM cycles, after vitrified-warmed embryo transfer, the ongoing clinical pregnancy rate per transfer was 7/22 (31.8%) (33). A larger study of 121 patients and 239 IVM cycles in which 3 days of FSH and no hCG was administered and oocytes were retrieved from follicles no larger than 6 mm, an ongoing clinical pregnancy rate of 9/24 (37.5%) after vitrified-warmed embryo transfer was reported (34). Pregnancy rate after fresh embryo transfer was significantly lower in both of these studies.

Subsequently, a "freeze-all" IVM strategy was used in a study of 79 PCOS patients, resulting in a cumulative live birth rate per patient of 17/78 (21.8%) (35). Further supporting the notion that freeze-all strategies are better for FSH priming of IVM cycles, a recent study showed a very high miscarriage rate after IVM when fresh transfers were compared with frozen-thawed embryo transfers (36.8% vs. 4.5%) (28). One thing to bear in mind with all of these studies is that there is a high level of attrition from retrieved immature COCs to good-quality blastocysts, owing in part to low maturation success after IVM. The chance of a single immature oocyte resulting in a live birth was only 1.1% (35). In addition, interpretation of these studies is complicated not only by significant variation in the stimulation protocols used, but also by inconsistent reporting of the stage of meiotic maturation of the oocytes at retrieval (GV vs. MI, as well as any mature MII oocytes recovered).

In Vitro Maturation and Cancer

IVM could be beneficial for patients desiring fertility preservation because of impending gonadotoxic cancer treatment (36). In one study, 248 breast cancer patients, aged 18–40 years, awaiting neoadjuvant chemotherapy were candidates for oocyte vitrification following IVM, at either the follicular or the luteal phase of the cycle (36). No major differences were seen in the number of oocytes retrieved or their IVM rates, whatever the phase of the cycle at which oocyte retrieval was performed, indicating that this novel use of IVM is clinically useful.

However, another study showed that vitrified-thawed IVM oocytes had a low survival rate (59.8%), lower fertilization and cleavage rates, and significantly lower pregnancy (10.7% vs. 36.1%) and take-home baby (8.9% vs. 25.9%) rates compared with fresh IVM oocytes (37). The authors concluded that the reproductive potential of vitrified IVM oocytes is impaired owing to the vitrification-warming procedure. Similarly, another study showed very poor pregnancy and delivery outcomes from vitrified-thawed embryos derived from IVM oocytes for cancer patients (38).

Moreover, IVM of oocytes after recovery from thawed ovarian tissue frozen from postmenarchal versus premenarchal girls yielded a low rate of maturity in both groups (28.2% vs. 15.5%, respectively), which was further reduced in girls under 5 years of age (4.9%) (39). Collectively, these studies highlight the need for more research targeting improvement of IVM media, as well as IVM protocols for premenarchal girls. Recent studies have shown that using antimüllerian hormone level and AFC information can help physicians to more accurately counsel patients on the potential likelihood of successful fertility preservation with the use of this approach (40, 41).

Oocyte Retrieval and Culture

There are no established criteria to identify the ideal timing or method for oocyte retrieval, with most studies using a lead follicular diameter of up to 10 mm (31, 42). Lead follicle diameters greater than 13 mm have been associated with reduced numbers of oocytes collected and matured (43), possibly related to subsequent atresia of the nondominant follicles from withdrawal of endogenous FSH support. Some protocols require an endometrial thickness of >5 mm while others do not include endometrial thickness as a criterion.

The aspiration technique differs for immature oocytes compared with mature oocytes retrieved in traditional IVF owing to the lack of cumulus cell expansion and tighter adherence of the immature oocyte to the follicle wall. Double-lumen needles to flush follicles have been described but do not appear to be necessary to retrieve immature oocytes (44). The optimal aspiration pressure and needle design have yet to be determined, with negative pressures ranging from 80 to 120 mm Hg and needle sizes ranging from 16 to 20 gauge (9, 31). Extremely high aspiration pressure has been shown to strip the oocyte of cumulus cells and negatively affect maturation and oocyte competence (45).

There is no consensus on the medium formulation that is best suited for IVM. Media typically simulate tissue culture medium, composed of high levels of glucose and normal levels of pyruvic and lactic acids, along with essential and nonessential amino acids and frequently supplemented with FSH and hCG/LH. Several versions are available commercially. A few studies on the improvement of IVM medium for human oocytes have been reported, but significantly more research is needed in this area.

A recent development in IVM is the inclusion of a prematuration (pre-IVM) step. Some commercial IVM media have historically included a short (2 hour) preincubation step before moving the eggs into the IVM medium. However, pre-IVM medium contains reagents, such as forskolin, and/or C-type natriuretic peptide, to block meiotic resumption and maintain oocytes at the GV stage for up to 24 hours until they are moved into IVM medium. This strategy is designed to better support oocyte cytoplasmic maturation and improve oocyte competence after IVM. The first report of human IVM including this pre-IVM step and improved IVM medium containing amphiregulin and FSH reported an increase in oocyte maturation after IVM, as well as an increase in good-quality blastocysts (46).

Chromosome constitution, and DNA methylation and expression of imprinted genes, in embryos generated after pre-IVM/IVM appear to be normal (47, 48). A randomized controlled trial examined the effectiveness of pre-IVM versus standard IVM, defined as a short FSH stimulation without hCG administration. Results from that study suggested that in women with high AFC, those in the pre-IVM group had significantly higher maturation and clinical pregnancy rates, but both groups had similar live birth rates and neonatal outcomes (48).

Fertilization

In a randomized control trial of standard insemination versus intracytoplasmic sperm injection (ICSI) for sibling IVM oocytes from patients with PCOS, there was no difference reported for all outcomes measured, including fertilization rates and blastocyst development (49). Although IVF can readily be used to fertilize IVM oocytes, ICSI has been advocated as the preferred method. However, although fertilization rates appear to be increased with the use of ICSI for IVM oocytes, developmental competence may be impaired, as demonstrated in one comparative trial (27).

The fertilization success rate of matured oocytes in patients who did not receive gonadotropins was only 37.7% (229/608 matured oocytes) with the use of conventional IVF compared with 69.3% (318/459 mature oocytes) when ICSI was used. Despite lower fertilization results, the implantation rate was significantly higher in embryos derived from oocytes fertilized with the use of conventional IVF versus ICSI (24.2% vs. 14.8%; $P<.05$) as was the clinical pregnancy rates per embryo transfer (34.5% vs. 20.0%; $P<.05$) (27). However, with the more recent adoption of preimplantation genetic testing for aneuploidies (PGT-A) in many laboratories, ICSI is often the fertilization method of choice. In addition, PGT-A provides some confidence before embryo transfer that IVM-produced embryos are, at minimum, chromosomally normal (50).

In Vitro Maturation: Safety Concerns

Scientific studies on the safety of IVM did not demonstrate an increase in imprinting errors after IVM (51), and cellular morphology in IVM oocytes does not differ from in vivo matured oocytes according to transmission electron microscopy (52). The neonatal health and developmental outcome of children conceived with the use of IVM has been studied in small numbers and are thus far reported to be no different than children born through traditional IVF with or without ICSI (53–57). However, the relatively small number of children conceived through IVM compared with IVF limits the accuracy of malformation and anomaly rates, and developmental outcomes cannot yet be adequately assessed.

SUMMARY

- Stimulation protocols with no FSH or short FSH stimulation, followed by hCG priming of intermediate follicles or no hCG, can be successfully used to retrieve oocytes for clinical human IVM. Most recent work in this area has focused on a 3-day stimulation with FSH, with or without hCG administration, and retrieval of oocytes from small follicles. In studies that manipulate the timing of meiotic maturation in vitro to improve oocyte competence, only FSH is used.
- A high level of attrition from oocyte to blastocyst is observed in IVM, owing in large part to suboptimal nuclear and cytoplasmic maturation. There is a clear need for more research in this area to increase the efficiency of IVM for clinical application.
- The use of ICSI is typically, but not always, combined with the use of IVM. At this time, vitrification of immature oocytes is not recommended owing to reports of poor outcomes.
- Because a relatively small number of children have been conceived with the use of IVM, information on the safety of IVM regarding malformation and developmental outcomes cannot yet be fully assessed. However, initial studies are reassuring.

CONCLUSIONS

- Candidates for IVM may include women at risk for OHSS, including women with PCOS or PCO-like ovaries. Efficacy of IVM in the context of estrogen-sensitive cancers, or in women with limited time for initiating fertility preservation before undergoing potentially gonadotoxic cancer treatments, is still not clear.
- IVM provides an alternate treatment protocol for these groups of women, with reduced patient burden due to shorter stimulation cycles, fewer injections, and associated reduced drug and monitoring costs.
- IVM should be offered by those with expertise gained by specific training, and should always be accompanied by appropriate counseling about expected results and informed consent. This technology is no longer considered experimental.
- IVM is not applicable to every patient; only those with a high AFC are good candidates. However, at this time, patients should be made aware that blastocyst conversion is lower and that implantation and pregnancy rates may be reduced compared with conventional IVF.
- Large trials comparing clinical outcomes of promising newer methods of IVM versus standard IVF, as well as long-term follow-up studies of neonatal health and developmental outcomes of offspring, are necessary.

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Maduración in vitro: opinión de un comité.

Los resultados de las investigaciones en maduración in vitro (MIV) sugieren la posibilidad de una aplicación clínica más amplia. Este documento analiza la eficacia de MIV según lo informado en la literatura publicada hasta la fecha. Este documento reemplaza al documento del mismo nombre, publicado por última vez en 2013.