









# 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](http://www.asco.org/survivorship-guidelines).

## ACCOMPANYING CONTENT

 Listen to the podcast by Dr Harvey, Dr Su, and Dr Loren at <https://ascopubs.org/doi/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.

## 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), oophorectomy, 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.

## 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.<sup>1</sup> Despite the recognized importance of FP, there remains a need for consistent, current, evidence-based guidance for health care clinicians.<sup>2</sup> Patients often do not receive adequate information or timely referrals to fertility specialists before initiating cancer-directed therapy.<sup>3,4</sup> 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<sup>5</sup> and 2018.<sup>6</sup> 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.

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.<sup>7,8</sup> 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](http://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,<sup>9-21</sup> 65 systematic reviews,<sup>22-40,41-60,61-86</sup> 6 RCTs,<sup>87-93</sup> and 82 observational studies<sup>94-110,111-130,131-150,151-175</sup> 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.<sup>176</sup> 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.<sup>177</sup> 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

**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 reseeded unknown; reproductive potential uncertain; uncertain storage costs

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

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.<sup>65,99</sup> 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.<sup>65,94,100-102,178</sup> Information that addresses perceived unmet needs specific to infertility risk and FP is most helpful when provided in a standardized and written format.<sup>65</sup>

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.<sup>95,97,98</sup> 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.<sup>96</sup>

## 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.<sup>23,71,72,76,103,116,179</sup> Combining alkylating agents with pelvic radiation further increases these risks. Platinum exposure also heightens the risk of POI and reduced ovarian reserve.<sup>76,103</sup> Radiation exposure ranging from 20 to 30 Gy or up to 15 Gy total body radiation can impair ovarian function.<sup>180</sup> 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.<sup>72,73,180-182</sup> The

**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% <sup>a</sup>	—	—	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]) <sup>83</sup>	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) <sup>84</sup> ; 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, gonadotropin-releasing hormone agonist; GYN, gynecologic; IVM, in vitro maturation; LBR, live birth rate; NA, not applicable; OHSS, ovarian hyperstimulation syndrome; OTC, ovarian tissue cryopreservation.

<sup>a</sup>Rate reported in a review of 18 patients, with three pregnancies out of five that tried.<sup>85</sup>

**TABLE 3. Summary of Fertility Preservation Recommendations**

Overarching Topic	Recommendation
<p><i>General Note.</i> 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.</p>	
Discussing risk of infertility with patient	<p>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)</p> <p>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)</p> <p>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)</p> <p>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)</p> <p><i>Qualifying Statement for Recommendations 1.3 and 1.4:</i> 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.</p>
Risks of infertility from cancer treatment	<p>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)</p>
Fertility preservation in males	<p>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)</p> <p><i>Qualifying Statement for Recommendation 3.1:</i> 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.</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>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)</p>
Fertility preservation in females	<p>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)</p> <p>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)</p> <p><i>Qualifying Statements for Recommendations 4.1 and 4.2:</i>  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</p>

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TABLE 3. Summary of Fertility Preservation Recommendations (continued)

Overarching Topic	Recommendation
	<p>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.</p>
	<p>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)</p>
	<p><i>Qualifying Statement for Recommendation 4.3:</i> 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.</p>
	<p>4.4. In vitro maturation (IVM): IVM of oocytes may be offered as an emerging FP method. (Evidence quality: Low; Strength of recommendation: Conditional)</p>
	<p><i>Qualifying Statement for Recommendation 4.4:</i> 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.</p>
	<p>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)</p>
	<p><i>Qualifying Statement for Recommendation 4.5:</i> Ovarian transposition is not suitable for patients with a moderate or high risk of ovarian metastasis, or those receiving concomitant gonadotoxic chemotherapy.</p>
	<p>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)</p>
	<p>4.7. Conservative gynecologic surgery:</p> <ol style="list-style-type: none"> <li>For patients with stage IA2 to IB1 cervical cancer, radical trachelectomy may be offered to preserve fertility if the tumor diameter is &lt;2 cm and invasion depth is &lt;10 mm</li> <li>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.</li> <li>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.</li> <li>In other gynecologic malignancies, less radical surgeries may be offered to spare reproductive organs when clinically appropriate. (Evidence quality: Moderate; Strength of recommendation: Strong)</li> </ol>
	<p><i>Qualifying Statement for Recommendation 4.7:</i> 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.</p>
	<p>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)</p>
	<p>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)</p>
	<p>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)</p>
	<p><i>Qualifying Statement for Recommendation 4.10:</i> 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.</p>
Fertility preservation in children	<p>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)</p>

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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.

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.<sup>73</sup> Higher radiation doses to the uterus (≥12 Gy) are associated with uterine toxicity and restricted fetal growth during pregnancy.<sup>73</sup> 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.<sup>104,105</sup> 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.<sup>183–185</sup>

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.<sup>152</sup> Alkylating chemotherapy, platinum agents, radiation to the testes, and hematopoietic cell transplants are particularly harmful to spermatogenesis.<sup>20,23,106–108,154,186</sup> While lower doses of testicular radiation and unilateral orchiectomy have less long-term impact, consensus on risk stratification cut points is lacking.<sup>179</sup> 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.<sup>185</sup>

The Children's Oncology Group recently reviewed phase III clinical trials to assess the gonadotoxic risks associated with standard chemotherapy regimens.<sup>109,110</sup> 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<sup>2</sup> in males or >8 g/m<sup>2</sup> and 12 g/m<sup>2</sup> in pubertal and prepubertal females, respectively, be classified as high risk.<sup>187</sup>

### 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<sup>26</sup> and two observational studies,<sup>117,118</sup> 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.<sup>26</sup> 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.<sup>118</sup> 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.<sup>117</sup> Compared to those without cancer, sperm quality was lower in patients with cancer before treatment ( $P = .01$ ) and further decreased after treatment ( $P = .001$ ).<sup>117</sup> 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 ( $P = .829$ ).<sup>117</sup>

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.<sup>188</sup> 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<sup>40</sup> and three additional studies<sup>119–121</sup> 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.<sup>40</sup> 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 ( $P > .05$ ).<sup>40</sup>

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.<sup>119</sup> 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.<sup>120</sup> 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.<sup>121,153,156,179</sup> One retrospective analysis of 97 survivors of cancer found a successful retrieval and cryopreservation rate of 50.7% in patients with

nonobstructive azoospermia and 100% in patients affected by retrograde ejaculation or failure of emission.<sup>156</sup>

## 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<sup>17</sup> and international guidance.<sup>12,14</sup>

## 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.<sup>10,12,17,189-191</sup>

## Risks to Sperm

### Literature Review Update and Analysis

Updated evidence<sup>106,192</sup> 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.<sup>106</sup> Alkylating agents and radiation can induce a high risk of mutations in spermatozoa produced within 1-2 weeks after initiation of therapy.<sup>192</sup> Topoisomerase II inhibitors, and potentially microtubule inhibitors, pose the greatest risk between weeks 5 and 7 of treatment.<sup>192</sup> Nucleoside analogs, antimetabolites, and bleomycin induce mutagenic effects on spermatozoa during weeks 7-10 of therapy.<sup>192</sup>

## 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.<sup>13,34,48,77,87,88,123,124,158,193</sup>

**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.<sup>34</sup> 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.<sup>34</sup>

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.<sup>13,124</sup> 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.<sup>13,123,193</sup> Risk of OHSS can be mitigated by GnRH agonist triggers in lieu of high-dose human chorionic gonadotropin (hCG) triggers.<sup>161,162</sup>

**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.<sup>77</sup> While reducing peak estradiol levels, these alternative protocols did not impact the number of oocytes or embryos retrieved.<sup>87</sup> In a

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 ( $12 \pm 8.6$  v  $11.6 \pm 7.5$ ,  $P = .81$  [95% CI of difference,  $-2.9$  to  $3.7$ ]).<sup>88</sup> 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.<sup>158</sup>

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.<sup>48</sup> 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]).<sup>48</sup> 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]).<sup>48</sup>

## 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.<sup>30,33,37,47</sup>

### Efficacy

#### Pregnancy and LBR

A meta-analysis of nine studies on pregnancies resulting from embryo cryopreservation found a pooled pregnancy rate of 49.0%.<sup>47</sup> The corresponding LBR was 35.3%.<sup>47</sup> 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.<sup>37</sup>

### 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%).<sup>37</sup> Another meta-analysis of six studies found the pooled miscarriage rate of 16.9%, based

on the cumulative number of miscarriages per embryo transfer.<sup>47</sup> Additionally, a systematic review reported a miscarriage rate of 20%.<sup>30</sup>

## Mature Oocyte Cryopreservation

### Literature Review Update and Analysis

The updated literature search identified six systematic reviews ± meta-analyses<sup>30,33,34,37,47,48</sup> investigating oncologic, reproductive, and safety outcomes of cryopreservation of unfertilized oocytes and an additional six studies<sup>88,122,123,126,127,193</sup> 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%.<sup>47</sup>

#### LBR After Oocyte Vitrification

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

### Risks

#### Miscarriage

Eight studies involving 177 females were analyzed for miscarriage after IVF with vitrified oocytes.<sup>37</sup> 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  $-0.00$ ]).<sup>78</sup>

#### 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.<sup>129</sup> These findings are consistent with older reports of a congenital anomaly incidence of 1.3%.<sup>128</sup> Furthermore, when compared to fresh oocytes, long-term cryopreservation does not appear to result in an increased occurrence of embryonic aneuploidy.<sup>150</sup>

## 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,<sup>125,131,151,159,163</sup> 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.<sup>155,179</sup> 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.<sup>179</sup> AMH trajectories indicate a possible timing window for FP for some but not all survivors.<sup>160</sup>

For females desiring FP soon after start of cancer therapy, successful ovarian stimulation and oocyte retrievals have been reported,<sup>131,151,167,169</sup> 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 pre-treatment 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,<sup>9,13–15,17</sup> systematic reviews and meta-analyses,<sup>18,34,57,58,60,62,64,70</sup> randomized trials,<sup>90–93</sup> and observational studies<sup>130,132,133</sup> 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.<sup>18,58,62,64,70,90,92,133,194</sup> However, evidence supporting

improved fertility outcomes for most types of cancer or in females receiving other systemic cancer-directed treatments remains limited.<sup>57,58,60,62,70,93</sup> 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;  $P = .03$ ).<sup>58</sup> 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.<sup>195</sup> Furthermore, only one trial<sup>93</sup> 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.<sup>9,58,60–62,70</sup> 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,<sup>43,45,75</sup> one RCT,<sup>89</sup> and 16 observational studies<sup>134–141,144,145,148,164–166,168,170</sup> 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.<sup>75</sup> 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.<sup>75</sup>

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

maturation (OTO-IVM) was investigated in a systematic review that included 12 studies involving prepubertal and postpubertal females with cancer.<sup>43</sup> 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.<sup>43</sup> Furthermore, 118 embryos were obtained following IVF or ICSI, with a mean fertilization rate of 64.5% in post-IVM oocytes.<sup>43</sup>

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).<sup>137</sup> This resulted in a mean of  $7.6 \pm 5.7$  oocytes vitrified in OTO-IVM and  $4.6 \pm 4.9$  in OPU-IVM, compared to  $6.8 \pm 4.6$  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.<sup>144</sup> Another study showed successful oocyte and blastocyst vitrification from oophorectomy samples, especially in younger patients with higher AMH levels.<sup>135</sup> 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 ( $1.39 \pm 2.48$  per patient,  $P < .05$ ).<sup>148</sup> However, the fertilization and embryo development rates of IVM oocytes were comparable to those of in vivo matured oocytes.<sup>148</sup> Some limitations were identified, such as the presence of ovarian cysts, which could reduce the number of mature oocytes in OTO-IVM procedures.<sup>134</sup> 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.<sup>89,136,168</sup>

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

## 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.<sup>31,52,67,79</sup>

## 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.<sup>31</sup> 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.<sup>79</sup> 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<sup>142</sup> 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  $\pm$  brachytherapy group, and 61% (95% CI, 55% to 69%) in the external-beam pelvic radiotherapy  $\pm$  brachytherapy  $\pm$  surgery group.<sup>67</sup> 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.<sup>52</sup> 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.<sup>197</sup>

### 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.<sup>31</sup> 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.<sup>147</sup> 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.<sup>146</sup> 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%).<sup>146</sup> Additional

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%,  $P = .003$ ).<sup>79</sup>

## 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 post-surgical adhesions.<sup>52</sup> 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 intra-operative complications were reported.<sup>31</sup>

### Metastases

Among patients with cervical cancer undergoing OT, the incidence of ovarian metastasis is reported to be 0.4%.<sup>52</sup>

## 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.<sup>24,85</sup>

### 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.<sup>85</sup> 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.<sup>85</sup>

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.<sup>24</sup> 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.<sup>24</sup>

### 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,<sup>29,32,35,39,41,42,46,50,51,54,59,63,66,80,143,171</sup> five on ovarian cancer,<sup>27,38,53,68,81</sup> one on early-stage endometrial cancer,<sup>25</sup> and two on gynecologic cancers in general.<sup>49,86</sup>

### Efficacy

**Reproductive outcomes.** A systematic review<sup>49</sup> 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%.<sup>41</sup> 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.<sup>41</sup> 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.<sup>54</sup> 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%).<sup>80</sup> 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.<sup>35</sup> Additional systematic review evidence indicates the lowest pregnancy rate is observed in patients undergoing radical trachelectomy by laparotomy (36%).<sup>42</sup>

In patients with early-stage cervical cancer  $\geq 2$  cm, surgery-based fertility-sparing treatment showed a pregnancy rate of 18%–22%, birth rate of 11%, and preterm rate of 10%.<sup>29,32</sup> 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 ( $P < .001$ ).<sup>32</sup>

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).<sup>39</sup>

**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).<sup>38</sup>

**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.<sup>25</sup>

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

### Oncological Outcomes

A systematic review<sup>49</sup> 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<sup>143</sup> and ovarian cancers,<sup>27</sup> but higher for endometrial cancer, indicating a heightened need for careful patient selection.<sup>198</sup>

**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.<sup>41</sup> 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%.<sup>42</sup> In patients having a stage IB2 disease, the recurrence rate after radical trachelectomy by laparotomy was 4.8% ( $P = .0035$ ).<sup>42</sup> 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.<sup>35</sup> Other meta-analyses<sup>66</sup> 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.<sup>21</sup> 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.<sup>80</sup> 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.<sup>174</sup> Patients with tumors larger than 2 cm had a threefold higher risk of recurrence than those with smaller tumors, irrespective of the treatment radicality.<sup>174</sup>

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.<sup>39</sup> 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.<sup>46,50,51,59,63,171</sup>

**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]).<sup>38</sup> 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];  $P = .84$ ).<sup>68</sup> Data on disease-free survival also indicated no difference

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.<sup>68</sup> Evidence from other systematic reviews<sup>27,53,86</sup> 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%).<sup>25</sup> Additional evidence for oncologic outcomes in patients with endometrial cancer is consistent with these findings,<sup>86</sup> although a pooled relapse rate of 20% with fertility-preserving treatment has recently been reported.<sup>25</sup>

There is emerging evidence on including molecular classification to enhance assessment and treatment strategies for young women seeking fertility-sparing treatment options.<sup>199</sup> 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<sup>30,36,37,44,47,55,56,69,74,82,84,149</sup> and six additional observational studies<sup>111–114,172,175</sup> 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.<sup>149</sup> 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.<sup>55</sup> Return to menstruation was reported to take place between 2 months and 1 year after transplantation.<sup>55</sup> A meta-analysis also considered the restoration rate of ovarian function and included a total of 12 studies involving 499 females.<sup>37</sup> While seven articles reported a 100% restoration rate, analysis of the outcome “no

ovarian function restoration” revealed a rate of 6%.<sup>37</sup> Another meta-analysis found menstrual activity outcomes were reported for 273 females assessed in the included trials.<sup>44</sup> 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.<sup>44</sup> 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).<sup>111</sup> 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.<sup>172</sup>

Importantly, the return of menstrual activity appeared to align closely with the restoration of hormonal function.<sup>44</sup> 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.<sup>44</sup>

**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.<sup>47</sup> 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.<sup>173</sup> 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.<sup>173</sup> 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.<sup>173</sup>

**LBR after OTC.** Examining LBR following IVF after OTC, eight studies involving 266 females were analyzed in a meta-analysis.<sup>37</sup> 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%.<sup>47</sup>

**Pregnancy after OTT.** Evidence from a systematic review of 25 studies indicates that 52% of patients reported pregnancy after OTT,<sup>55</sup> with another systematic review of 20 studies finding 62.5% of females had one or more pregnancies.<sup>56</sup> 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.<sup>56</sup>

Pregnancy after OTT was further assessed in a meta-analysis of 18 studies and 547 females.<sup>44</sup> 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.<sup>149</sup> The pregnancy rate for frozen-thawed ovarian tissue transplants was 37% (95% CI, 32% to 43%).<sup>44</sup> 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%,<sup>44</sup> 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.<sup>44</sup> 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.<sup>44</sup> 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.<sup>111</sup>

**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.<sup>30</sup> 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.<sup>56</sup> Live births after OTT were further assessed in a meta-analysis incorporating 17 studies and 539 females.<sup>44</sup> 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%).<sup>37</sup>

## Risks

**Miscarriage.** A meta-analysis examining miscarriage following OTT pooled data from 10 studies involving 436 females.<sup>37</sup> 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.<sup>47</sup> Another meta-analysis of 15 studies found the miscarriage rate for frozen transplants was 37% (95% CI, 30% to 46%).<sup>44</sup> Moreover, the pooled evidence from this meta-analysis found that significantly fewer miscarriages occurred with OTC than with embryo cryopreservation.<sup>47</sup> 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.<sup>36</sup> 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.<sup>36</sup> Older systematic review evidence from 42 studies and 422 patients found that 7% raised suspicion of malignant cell infiltration.<sup>74</sup> A more recent review identified two reports of cancers occurring within transplanted ovarian grafts.<sup>44</sup> 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.<sup>175</sup> Screening confirmed no malignant cells in the ovarian tissue before transplantation, and patients remained relapse-free over a median follow-up of 51 months.<sup>175</sup> 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.<sup>113,114,158</sup>

**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.<sup>82,112,149</sup> 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.<sup>69</sup> 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.<sup>82</sup> 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.<sup>82</sup>

## 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,<sup>9-12,16,19</sup> seven reviews,<sup>23,28,179,200-203</sup> and four additional observational studies<sup>108,113,115,185</sup> 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.<sup>11,16</sup>

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<sup>17</sup> and the American Academy of Pediatrics,<sup>19</sup> among others,<sup>11</sup> 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.<sup>16,202</sup> Furthermore, the risk of reintroducing malignant cells during tissue transplantation is a significant concern, especially for

patients with hematologic cancers.<sup>113</sup> Strategies to ensure the safe use of cryopreserved tissues are under development.<sup>16,185</sup>

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.<sup>16,185</sup> 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.<sup>28</sup>

#### 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.<sup>26</sup> 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.<sup>5,16</sup> 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.<sup>23,108</sup> Despite being experimental, TTC holds promise, as animal studies have demonstrated the restoration of spermatogenesis and the production of viable offspring following transplantation.<sup>108</sup>

Studies emphasize the risks of alkylating agents on male fertility, particularly in prepubertal males.<sup>108</sup> Research underscores the importance of preserving spermatogonial cells before cancer treatment begins, as these treatments can severely impact spermatogenesis.<sup>108</sup> 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.<sup>115</sup>

#### 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.

## 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.<sup>202</sup> 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.<sup>204,205</sup>

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.<sup>206</sup> 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.<sup>207</sup> 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.<sup>9-12,14,15</sup> 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.<sup>22</sup> 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.<sup>208</sup>

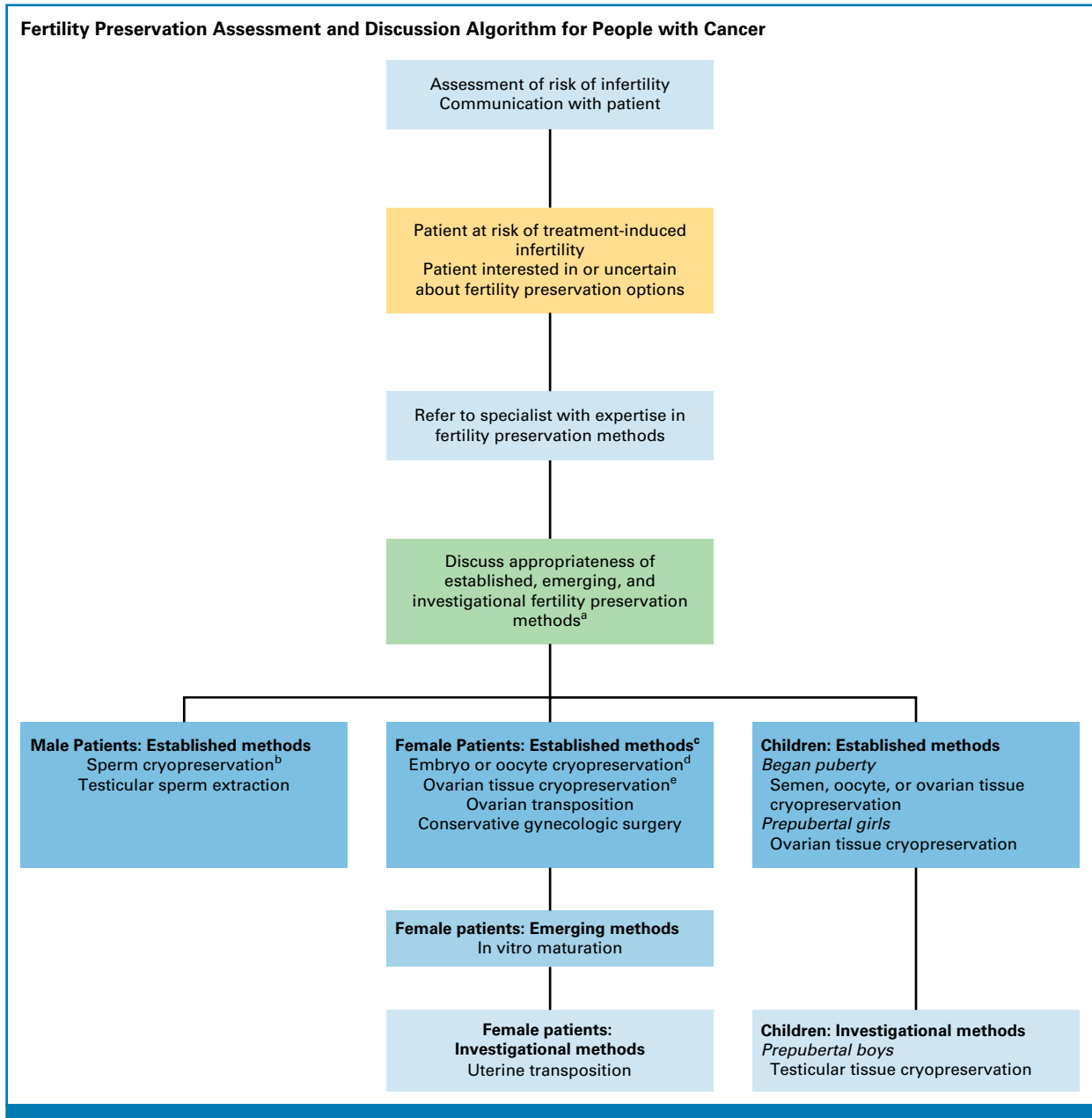
For people with cancer who are unable to pursue biological parenthood post-treatment, other family-building options like gestational carriers, oocyte, sperm, and embryo donation, and adoption are available. Psychosocial providers can assist patients and families in the decision-making process about FP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

## 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.

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](http://www.asco.org/survivorship-guidelines). <sup>a</sup>Patients and fertility clinics should investigate whether the patient’s plan covers FP services and where they can receive in-network services. <sup>b</sup>Some patients may proceed with this without the prior step of seeing a reproductive specialist. However, consultation with reproductive specialist is recommended. <sup>c</sup>GnRHa may be offered as an adjunct in females with breast cancer or for patients with oncologic emergencies requiring urgent chemotherapy. <sup>d</sup>May also be offered in the post-treatment setting. <sup>e</sup>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](mailto: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.<sup>210</sup> Other research is focusing on adjuvant fertoprotective agents aimed at preventing follicle loss after chemotherapy-induced damage.<sup>211</sup> In young male cancer survivors, experimental strategies like SSC transplantation may also hold promise for future FP.<sup>26</sup> 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, non-existent, 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 be 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.<sup>212</sup>
- 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.

## 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.<sup>213</sup>

## 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.<sup>214,215</sup> 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.<sup>216</sup> 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.<sup>217</sup>

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.<sup>100,178</sup> Participants in minoritized groups also reported unclear communication and prohibitive costs.<sup>94</sup> Moreover, females with lower education

levels, older age, and those with less common cancers are less likely to be counseled.<sup>100,218</sup> 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.<sup>219</sup> Additionally, sexual and gender minority populations experience stigma along with barriers to cancer screening, prevention, and treatment that contribute to these cancer disparities.<sup>220</sup> Disparities widen in those who are also from a racial or ethnic minority, underscoring the influence of intersectionality in cancer health disparities.<sup>221</sup>

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.<sup>222</sup>

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.<sup>223,224</sup> Higher patient out–of–pocket costs have been shown to be a barrier to initiating and adhering to recommended treatments.<sup>225,226</sup> Utilization of FP treatments is associated with medical financial hardship.<sup>227</sup>

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.<sup>228</sup> 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.

Discussion of cost can be an important part of shared decision-making.<sup>229</sup> 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.<sup>229</sup>

## 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 front-line 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](http://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](http://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](http://www.asco.org/guideline-methodology)) provides additional information about the methods used to develop this guideline. Patient information is available at [www.cancer.org](http://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](mailto:guidelines@asco.org). Comments may be incorporated into a

## RELATED ASCO GUIDELINES

- Patient-Clinician Communication<sup>213</sup> (<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<sup>230</sup> (<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<sup>231</sup> (<https://ascopubs.org/doi/10.1200/JGO.2016.003954>)
- Interventions to Address Sexual Problems in People with Cancer<sup>232</sup> (<https://ascopubs.org/doi/10.1200/JCO.2017.75.8995>)
- Management of Anxiety and Depression in Adult Survivors of Cancer<sup>233</sup> (<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<sup>234</sup> (<https://ascopubs.org/doi/10.1200/OP.23.00716>)

future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at [www.asco.org/guidelines](http://www.asco.org/guidelines).

## GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.<sup>235</sup> 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.<sup>236-239</sup> 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](http://www.cancer.org), is available at [www.asco.org/survivorship-guidelines](http://www.asco.org/survivorship-guidelines).

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### Fertility Preservation in People With Cancer: ASCO Guideline Update

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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## APPENDIX 1. GUIDELINE DISCLAIMER

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## APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at <http://www.asco.org/guideline-methodology>). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

**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, FRCPC	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)

**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.<sup>240</sup>

Abbreviation: FP, fertility preservation.