

## Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Alison W. Loren, Pamela B. Mangu, Lindsay Nohr Beck, Lawrence Brennan, Anthony J. Magdalinski, Ann H. Partridge, Gwendolyn Quinn, W. Hamish Wallace, and Kutluk Oktay

### ABSTRACT

#### Purpose

To update guidance for health care providers about fertility preservation for adults and children with cancer.

#### Methods

A systematic review of the literature published from March 2006 through January 2013 was completed using MEDLINE and the Cochrane Collaboration Library. An Update Panel reviewed the evidence and updated the recommendation language.

#### Results

There were 222 new publications that met inclusion criteria. A majority were observational studies, cohort studies, and case series or reports, with few randomized clinical trials. After review of the new evidence, the Update Panel concluded that no major, substantive revisions to the 2006 American Society of Clinical Oncology recommendations were warranted, but clarifications were added.

#### Recommendations

As part of education and informed consent before cancer therapy, health care providers (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons) should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, the Update Panel encourages providers to advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation. The discussion should be documented. Sperm and embryo cryopreservation as well as oocyte cryopreservation are considered standard practice and are widely available. Other fertility preservation methods should be considered investigational and should be performed by providers with the necessary expertise.

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### INTRODUCTION

In 2006, the American Society of Clinical Oncology (ASCO) published a clinical practice guideline on fertility preservation for adults and children with cancer.<sup>1</sup> ASCO guidelines are updated periodically by a subset of the original Expert Panel. In October 2012, the Update Panel reviewed the results of a systematic review of the new literature and determined that although the recommendations remained the same (with the exception of adding oocyte cryopreservation as a standard practice, whereas in the previous guideline, it was still considered experimental), some information and tables needed to be updated. In terms of who is responsible

for discussing fertility preservation, the original language used by ASCO has been revised: The word “oncologist” was replaced with “health care provider” to include medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons, as well as nurses, social workers, psychologists, and other nonphysician providers.

### GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions: (1) Are patients with cancer interested in interventions to preserve fertility?

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## THE BOTTOM LINE

### Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

#### **Intervention**

- Discuss the risk of infertility and fertility preservation options with patients with cancer anticipating treatment

#### **Target Audience**

- Medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons, as well as nurses, social workers, psychologists, and other nonphysician providers

#### **Key Recommendations**

- Discuss fertility preservation with all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy
- Refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists
- Address fertility preservation as early as possible, before treatment starts
- Document fertility preservation discussions in the medical record
- Answer basic questions about whether fertility preservation may have an impact on successful cancer treatment
- Refer patients to psychosocial providers if they experience distress about potential infertility
- Encourage patients to participate in registries and clinical studies

#### **Adult Males**

- Present sperm cryopreservation (sperm banking) as the only established fertility preservation method
- Do not recommend hormonal therapy in men; it is not successful in preserving fertility
- Inform patients that other methods (eg, testicular tissue cryopreservation, which does not require sexual maturity, for the purpose of future reimplantation or grafting of human testicular tissue) are experimental
- Advise men of a potentially higher risk of genetic damage in sperm collected after initiation of chemotherapy

#### **Adult Females**

- Present both embryo and oocyte cryopreservation as established fertility preservation methods
- Discuss the option of ovarian transposition (oophoropexy) when pelvic radiation therapy is performed as cancer treatment
- Inform patients of conservative gynecologic surgery and radiation therapy options
- Inform patients that there is insufficient evidence regarding the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method, and these agents should not be relied on to preserve fertility
- Inform patients that other methods (eg, ovarian tissue cryopreservation, which does not require sexual maturity, for the purpose of future transplantation) are still experimental

#### **Children**

- Use established methods of fertility preservation (semen cryopreservation and oocyte cryopreservation) for postpubertal minor children, with patient assent, if appropriate, and parent or guardian consent
- Present information on additional methods that are available for children but are still investigational
- Refer for experimental protocols when available

#### **Methods**

- A comprehensive systematic review of the literature was conducted, and an Update Panel was convened to review the evidence and guideline recommendations

#### **Additional Information**

Data Supplements (including evidence tables) and clinical tools and resources can be found at <http://www.asco.org/guidelines/fertility>.

(2) What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males? (3) What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females? (4) What is the role of the oncologist in advising patients about fertility preservation options? Special considerations addressing the fertility needs of children with cancer are also addressed.

## RECOMMENDATIONS, CLINICAL TOOLS, AND RESOURCES

Table 1 provides the updated guideline recommendations. Clinical tools and resources, including links to related articles published in *Journal of Oncology Practice* and key Web sites, and Data Supplements are available at <http://www.asco.org/guidelines/fertility>, and a patient guide is available at <http://www.cancer.net>.

## METHODS

The Update Panel included academic and community practitioners, in the fields of adult and pediatric oncology, obstetrics-gynecology, reproductive endocrinology and infertility, health services research, and psychosocial oncology, as well as a patient advocate (Appendix Table A1, online only). The Update Panel completed a review and analysis of evidence (Data Supplements 1 and 2) published between March 2006 and January 2013 to determine whether the recommendations needed to be updated. The Update Panel drafted the guideline manuscript and submitted it for review. The ASCO Clinical Practice Guideline Committee then reviewed and approved the Updated Guideline.

Details of the literature search strategy are provided in Data Supplement 3. In brief, articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) The study discussed a fertility intervention and reported primary data, and (2) the study population consisted of patients with cancer scheduled for or undergoing cancer treatments that threaten fertility. Articles were excluded from further consideration if they did not report specifically on a fertility intervention and did not report primary data. However, because of the limited nature of the data in many areas, the Update Panel made an a priori decision to also retain high-quality reviews or background articles. A QUOROM diagram that reports the results of the literature search is available in Data Supplement 4.

### Guideline Policy

The practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not recommend any particular product or course of medical treatment. Use of the clinical practice guideline is voluntary.

### Guideline and Conflicts of Interest

The Update Panel was assembled in accordance with the ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (Procedures, summarized at <http://www.asco.org/guidelinescoi>). Members of the Update Panel completed a disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Panel did not disclose any such relationships.

## GUIDELINE RECOMMENDATIONS

After review and analysis of the evidence published since the original guideline appeared in *Journal of Clinical Oncology* in 2006, the Update Panel concluded that new evidence was not compelling enough to warrant substantive changes to any of the 2006 guideline recommendations. There were minor but significant changes worthy of attention; however, they did not necessitate a major revision of the guideline. Table 1 provides a summary of the 2013 guideline recommendations.

### Literature Search Results

There were 18 new randomized controlled trials,<sup>2-20</sup> six systematic reviews, meta-analyses, or previous guidelines,<sup>21-26</sup> and dozens of narrative reviews, case series and case studies, and editorials. Evidence tables are presented in Data Supplements 1 and 2.

### Limitations of the Literature and Future Research

Review of the fertility preservation literature revealed a paucity of large and/or randomized studies. Most data came from cohort studies, case series, small nonrandomized clinical trials, or case reports. Fertility preservation methods are still applied relatively infrequently in patients with cancer, limiting greater knowledge about the success and effects of different interventions and the long-term health of offspring. Insufficient attention is paid to the potential positive and negative effects, both physical and psychological, of fertility preservation. There is a need for research about decision making regarding the future use of cryopreserved tissue and posthumous reproduction.

Although there is current evidence that indicates a lack of effectiveness of hormonal suppression in fertility preservation, there is a need for a decisive study in which a large number of patients undergo follow-up involving sensitive ovarian reserve markers such as anti-Müllerian hormone and antral follicle counts as well as, if feasible, ovarian follicle counts assessed by histologic analysis of ovaries or by xenograft models with and without gonadotropin-releasing hormone agonist and antagonist (GnRHa) treatment during chemotherapy. The penultimate study should also have sufficient power and follow-up to compare pregnancy outcomes. Thus, the Update Panel encourages participation in clinical trials that meet these criteria as long as the patients also consider alternative and effective methods of fertility preservation.

In addition, little is known about the emotional impact of infertility or the use of fertility preservation options for people with cancer in ethnically, racially, or socioeconomically diverse groups, who may face even greater barriers to fertility preservation before treatment.

The Update Panel encourages additional well-designed studies evaluating methods of fertility preservation in people with cancer to help answer these questions. Research is also needed on the comparative effectiveness of different modes of fertility preservation. However, the Panel also acknowledges that the traditional gold standard of randomized, controlled, and blinded therapeutic studies may not be practical in this area. 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.

## UPDATE

This guideline update provides a brief review of key new studies under each clinical question addressing fertility preservation in adults and

**Table 1.** ASCO 2013 Recommendations for Fertility Preservation for Patients With Cancer

Clinical Question	Recommendation
1. Are patients with cancer interested in interventions to preserve fertility?  What can health care providers do to educate patients about the possibility of reduced fertility resulting from cancer treatments and to introduce them to methods to preserve fertility?	<p>1.1 People with cancer are interested in discussing fertility preservation. Health care providers caring for adult and pediatric patients with cancer (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, surgeons, and others) should address the possibility of infertility as early as possible before treatment starts.</p> <p>1.2 Health care providers should refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists.</p> <p>1.3 Fertility preservation is often possible, but to preserve the full range of options, fertility preservation approaches should be discussed as early as possible, before treatment starts. The discussion can ultimately reduce distress and improve quality of life. Another discussion and/or referral may be necessary when the patient returns for follow-up and if pregnancy is being considered. The discussions should be documented in the medical record.</p>
2. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males?	<p>2.1 Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.</p> <p>2.2 Hormonal gonadoprotection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.</p> <p>2.3 Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols.</p> <p>2.4 Postchemotherapy: Men should be advised of a potentially higher risk of genetic damage in sperm collected after initiation of 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 session. 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.</p>
3. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?	<p>3.1 Embryo cryopreservation: Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.</p> <p>3.2 Cryopreservation of unfertilized oocytes: Cryopreservation of unfertilized oocytes is an option, particularly for patients 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. As of October 2012, the American Society for Reproductive Medicine no longer deems this procedure experimental.  More flexible ovarian stimulation protocols for oocyte collection are now 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 old protocols. Thus, oocyte harvesting for the purpose of oocyte or embryo cryopreservation is now possible on a cycle day-independent schedule.</p> <p>3.3 Ovarian transposition: Ovarian transposition (oophoropexy) can be offered when pelvic irradiation is performed as cancer treatment. 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.</p> <p>3.4 Conservative gynecologic surgery: It has been suggested that radical trachelectomy (surgical removal of the uterine cervix) should be restricted to stage IA2 to IB cervical cancer with diameter &lt; 2 cm and invasion &lt; 10 mm.  In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery with the intent of sparing the reproductive organs as much as possible. Ovarian cystectomy can be performed for early-stage ovarian cancer.</p> <p>3.5 Ovarian suppression: Currently, there is insufficient evidence regarding the effectiveness of GnRHa and other means of ovarian suppression in fertility preservation.  GnRHa should not be relied upon as a fertility preservation method. However, GnRHa may have other medical benefits such as a reduction of vaginal bleeding when patients have low platelet counts as a result of chemotherapy. This benefit must be weighed against other possible risks such as bone loss, hot flashes, and potential interference with response to chemotherapy in estrogen-sensitive cancers. Women interested in this method should participate in clinical trials, because current data do not support it. In a true emergency or rare or extreme circumstances where proven options are not available, providers may consider GnRHa an option, preferably as part of a clinical trial.</p> <p>3.6 Ovarian tissue cryopreservation and transplantation: Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation or sexual maturity and hence may be the only method available in children. It is considered experimental and should be performed only in centers with the necessary expertise, under IRB-approved protocols that include follow-up for recurrent cancer.  A theoretic concern with reimplanting ovarian tissue is the potential for reintroducing cancer cells depending on the type and stage of cancer, although so far there have been no reports of cancer recurrence.</p> <p>3.7 Other considerations: Of special concern in estrogen-sensitive breast and gynecologic malignancies is the possibility that fertility preservation interventions (eg, ovarian stimulation regimens that increase estrogen levels) and/or subsequent pregnancy may increase the risk of cancer recurrence.  Ovarian stimulation protocols using the aromatase inhibitor letrozole have been developed and may ameliorate this concern. Studies do not indicate increased cancer recurrence risk as a result of subsequent pregnancy.</p>

(continued on following page)

**Table 1.** ASCO 2013 Recommendations for Fertility Preservation for Patients With Cancer (continued)

Clinical Question	Recommendation
4. What is the role of health care providers in advising patients about fertility preservation options?	4.1 All oncologic health care providers 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 before a treatment plan is formulated. There are benefits for patients in discussing fertility information with providers at every step of the cancer journey.
What should providers discuss with patients about fertility preservation?	4.2 Encourage patients to participate in registries and clinical studies, as available, to define further the safety and efficacy of these interventions and strategies 4.3 Refer patients who express an interest in fertility, as well as those who are ambivalent or uncertain, to reproductive specialists as soon as possible. 4.4 Refer patients to psychosocial providers when they are distressed about potential infertility.
5. Special considerations: Fertility preservation in children	5.1 Suggest established methods of fertility preservation (eg, semen or oocyte cryopreservation) for postpubertal minor children, with patient assent and parent or guardian consent. For prepubertal minor children, the only fertility preservation options are ovarian and testicular cryopreservation, which are investigational.

Abbreviations: ASCO, American Society of Clinical Oncology; GnRH<sub>a</sub>, gonadotropin-releasing hormone analog; IRB, institutional review board.

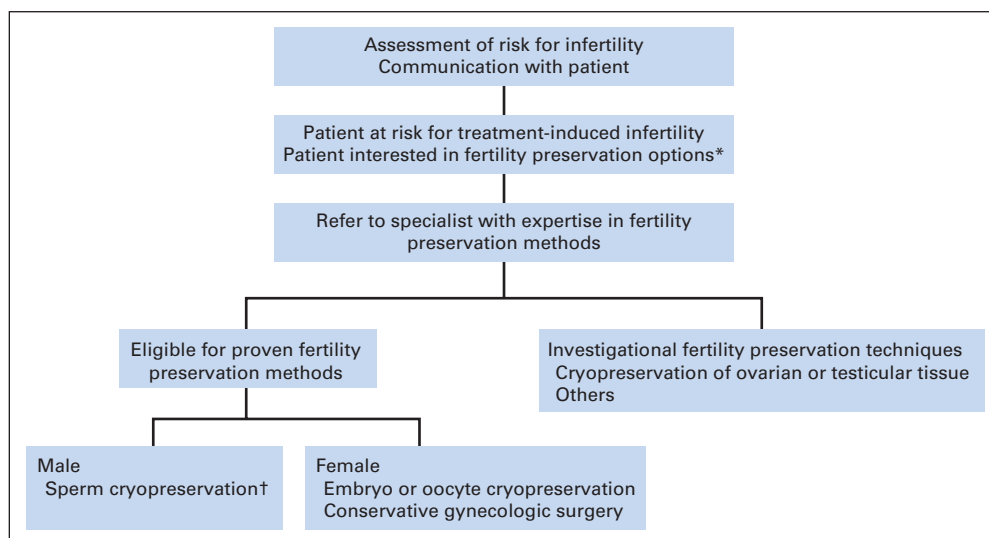
children undergoing treatment for cancer. The language has been clarified and/or strengthened in several recommendations. Information has been added to address role of psychosocial providers, fertility preservation concerns, and options for children and adolescents with cancer, as well as considerations for patients receiving targeted and biologic therapies in this update.

After a systematic review and analysis of the literature for the preservation of fertility for patients with cancer, the Update Panel concluded that there was no new evidence compelling enough to warrant substantial changes to any of the guideline recommendations. However, minor adjustments were made to reflect progress in the field (eg, oocyte cryopreservation is no longer investigational). Certainly, further research is needed to determine the true effectiveness of different modes of fertility preservation. More research is also needed to establish the best methods to disseminate information and to determine the best time to talk with patients about their options. The discussion should be a part of the comprehensive treatment planning process (Fig 1). The treatment planning discussion should include consideration of scientific evidence, weighing potential harms and benefits, reproductive potential, anticipated delay of childbearing, and patient preferences. The Update Panel strongly encourages health care

providers to have an open dialogue with patients or parents or guardians of children anticipating cancer treatment who express an interest in fertility preservation (and those patients who are ambivalent) and refer them as expeditiously as possible to a reproductive specialist, preferably before starting treatment. Electronic resources (eg, e-mail, Skype) are available that may facilitate novel methods of consultation, such as telephone- or Internet-based communication, for patients without geographic accessibility to these specialized providers.

**Are Patients With Cancer Interested in Interventions to Preserve Fertility?**

Current evidence suggests that discussions about fertility and fertility preservation are of great importance to patients with cancer.<sup>27</sup> It may be difficult for physicians to know how important fertility preservation is to their patients unless they ask, because many patients may not bring up the topic. The failure of patients to mention infertility concerns or interest in fertility preservation can result from a variety of factors; they may be overwhelmed by and focused exclusively on the cancer diagnosis,<sup>28</sup> they may be unaware that potential fertility loss may occur,<sup>29</sup> or they may be concerned that pursuing



**Fig 1.** Fertility preservation assessment and discussion algorithm for patients with cancer. (\*) Patients should be encouraged to contact their insurance company to ascertain out-of-pocket costs. (†) Some patients may proceed with this without the prior step of seeing a reproductive specialist. However, consultation with a reproductive specialist is recommended.

fertility preservation will delay their treatment, leading to increased morbidity or mortality.<sup>30</sup>

However, there is evidence to suggest that at least among women, patients may make cancer treatment decisions based on fertility concerns. In the study by Partridge et al,<sup>31</sup> 29% of women with breast cancer reported that infertility concerns influenced their treatment decisions.

### **What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Males?**

The treatment of cancer often poses a threat to male fertility. Understanding the effects of different antitumor agents on sperm production in men has changed little in the 7 years since the original guideline was published. An updated table on the effects of different antitumor agents on sperm production and a summary of fertility preservation options in males are presented in Data Supplement 5.

The Panel reviewed recent information supporting sperm cryopreservation, testicular hormonal suppression, and testicular tissue cryopreservation. The new evidence continues to support the conclusion that sperm cryopreservation is an effective method of fertility preservation in males treated for cancer.<sup>32-39</sup> In contrast, gonadoprotection through hormonal manipulation is ineffective. Testicular tissue or spermatogonial cryopreservation and transplantation or testis xenografting are still experimental and have not yet been successfully tested in humans. However, such approaches may be the only methods of fertility preservation potentially available to prepubertal boys. There are case reports and small case series of successful collection of sperm from a postmasturbation urine sample, rectal electroejaculation under anesthesia, and testicular sperm aspiration, but these remain uncommon and/or investigational. It also seems that testicular cryopreservation procedures can be combined with other medically indicated procedures to increase the feasibility and acceptability of these procedures.<sup>40</sup> The Update Panel notes that if patients are promptly referred to a fertility specialist, there is likely to be little to no significant delay in the initiation of cancer treatment.

### **What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Females?**

Understanding of the risks of permanent amenorrhea in women treated with modern chemotherapy and radiotherapy has changed little since the original guideline. However, there have been some advances in the science of fertility preservation that may affect patient decision making. An updated table on the risks of permanent amenorrhea in women treated with modern chemotherapy and radiotherapy and a summary of fertility preservation options in females is presented in Data Supplement 6.

The Panel reviewed the new literature supporting embryo and oocyte cryopreservation (with hormonal stimulation), ovarian transposition, surgical options other than radical trachelectomy, ovarian suppression, ovarian tissue cryopreservation and transplantation, and other considerations. Fertility preservation options in females depend on patient age, diagnosis, type of treatment, presence or participation of a male partner and/or patient preferences regarding the use of banked donor sperm, time available, and likelihood that cancer has metastasized to her ovaries. The Update Panel notes that because of requirements for scheduling and performing procedures, some (but

not all) interventions may entail a delay in cancer treatment and wishes to emphasize that early referral to a subspecialist can minimize this delay.

*Embryo cryopreservation.* New data indicate that although it is ideal to stimulate ovaries within 3 days of the start of the menstrual cycle, random stimulation can be successful as well.<sup>41</sup> This is an important and recent advance in the field of reproductive endocrinology. Furthermore, newer hormonal stimulation regimens (eg, letrozole and tamoxifen) may be effective as traditional methods, and their use may be preferred in women with hormone-sensitive cancers.<sup>3,6,12,42,43</sup>

Although aromatase inhibitors are primarily used as adjuvant treatment of hormone-positive breast cancers (in premenopausal women), they can act as ovarian stimulants yet suppress estrogen levels. As a result, letrozole has been used for ovulation induction in infertility patients and, in the last 10 years, for the purpose of ovarian stimulation for fertility preservation via oocyte or embryo cryopreservation in women with estrogen-sensitive cancer. When combined with standard fertility drugs, letrozole enhances ovarian stimulation while keeping estrogen levels near physiologic levels. Studies suggest that this approach results in similar numbers of eggs and embryos and similar pregnancy outcomes. Short-term follow-up indicated no impact on cancer-free survival. The Update Panel wishes to emphasize these developments because they may widen the opportunities for fertility preservation.

*Cryopreservation of unfertilized oocytes.* Success rates for this procedure have improved significantly, and it is no longer considered experimental by the American Society of Reproductive Medicine. Some reproductive specialty centers have reported success rates comparable to those obtained using unfrozen eggs, especially in younger women.<sup>9,44-46</sup> Like embryo cryopreservation, this technique also requires ovarian stimulation and ultrasound-guided oocyte retrieval. Oocyte cryopreservation is of particular importance for women who do not have a male partner or prefer not to use donor sperm.

*Ovarian suppression.* The question regarding the effectiveness of GnRHa is still not resolved. One recent study with flaws<sup>2</sup> cited a slight benefit for return of menstruation, but another article<sup>47</sup> showed no significant difference in the outcome point of chemotherapy-induced amenorrhea 6 months after the end of chemotherapy. A recent study demonstrated no benefit of using GnRHa in patients with breast cancer receiving cyclophosphamide-based chemotherapy.<sup>48</sup> In this study, no differences were observed in the menstruation resumption rates between GnRHa-treated patients versus the control group 12 months after termination of chemotherapy. Moreover, there were no differences in hormonal and ultrasound markers of fertility between patients receiving GnRHa and the control group. The use of GnRHa cotreatment did not predict independently the odds of menstruating at 12 months. Furthermore, a recent meta-analysis, which updates an earlier one, included 24 months of follow-up in the ZORO (Zoladex Rescue of Ovarian Function) study<sup>49</sup> and failed to demonstrate a possible beneficial effect of GnRHa use on either maintenance of menstruation or fertility. There are not definitive data<sup>5,11,21,50</sup> that show that GnRHa preserves fertility, and it remains the subject of ongoing research.

Given the current state of knowledge regarding these agents, it is the opinion of the Update Panel that GnRHa is not an effective method of fertility preservation. Furthermore, complete ovarian suppression is not achieved for several weeks after administration. However, there may be other potential benefits such as inhibiting menses

during intensive chemotherapy, thus preventing complications such as menorrhagia. In emergency, rare, or extreme circumstances, where proven options are not available, providers may consider GnRHa an unproven option (preferably as a part of a clinical trial), with special consideration of the patient's specific cancer and needs. This class of drugs also has adverse effects such as hot flashes and bone loss.

*Ovarian tissue cryopreservation and transplantation.* Although this process is still considered experimental, successful pregnancies have been reported. There is a theoretic concern with reimplanting ovarian tissue and the potential for reintroducing cancer cells depending on the type and stage of cancer, although so far there have been no reports of cancer recurrence in humans. In women who have survived cancer, at least 19 live births have been reported using cryopreserved ovarian tissue or oocytes.<sup>7,19,51-58</sup>

*Other considerations.* (1) With recent data supporting longer duration of hormonal therapies for estrogen receptor/progesterone receptor-positive breast cancer, larger numbers of women will be affected by the risk of compromised fertility.<sup>42</sup> These women will be older and thus at higher risk for infertility at the time that their hormonal therapy is completed. (2) It has been shown that *BRCA* mutation carriers, especially those with *BRCA1*, have diminished ovarian reserve.<sup>59</sup> There is a concern that *BRCA* mutation carriers may be more prone to chemotherapy-induced infertility as a result of already lower ovarian reserve and higher likelihood of low response to ovulation induction. This may be important when counseling women regarding their likelihood of infertility after chemotherapy. (3) For patients with inherited or familial cancers for which a mutation has been identified, there may be an added benefit of undergoing fertility preservation by oocyte or embryo cryopreservation, because embryos can be tested for these mutations by embryo biopsy, and preimplantation genetic diagnosis techniques can be considered. (4) A number of conservative surgical (eg, trachelectomy)<sup>60-64</sup> and radiation therapy approaches with the aim of preserving fertility are available but are not discussed further in this guideline. Surgical and radiation oncologists should discuss individualized approaches with specific patients, taking into account patient preferences, risks, specific tumor anatomy, and other concerns.

### **What Is the Role of the Health Care Provider in Advising Patients About Fertility Preservation Options? What Should Providers Discuss With Patients About Fertility Preservation?**

As with other potential complications of cancer treatment, all health care providers have a responsibility to inform patients about the risks that their cancer treatment will permanently impair fertility. Providers should encourage patients to look into insurance coverage (state-by-state differences) and out-of-pocket costs (which may be supported by charitable funding). An algorithm for triaging fertility preservation referrals is presented in Figure 1.

There are many new studies addressing the importance and timing of referral to reproductive specialists and psychosocial providers. Referrals should be made as soon as possible. Psychosocial providers such as social workers and psychologists can be particularly helpful when a patient is distressed about potential infertility. Some patients, after successful cancer treatment, may want to have a biologic child. The inability to conceive could be a great source of distress. Although it is ideal for a patient to discuss threats to fertility and potential options before cancer treatment, there are other family building

options that can be used postcancer. These include the use of gestational carriers, embryo donation, egg or sperm donation, and adoption. Psychosocial providers can assist patients and families in the decision-making process about fertility preservation and disposition of stored gamete options that are morally and ethically acceptable to them.<sup>29,34,65-87</sup>

Fertility preservation does not diminish the chance of successful cancer treatment. However, if a patient received a treatment that affects cardiopulmonary function, she should be evaluated by an appropriate specialist (eg, maternal-fetal medicine, cardiology, or pulmonology) before attempting pregnancy. If a woman underwent pelvic irradiation, this should be discussed with a maternal-fetal medicine specialist as well, because pregnancy complications such as intrauterine growth retardation and preterm delivery may occur as a result of uterine dysfunction.

### **Special Fertility Preservation Considerations for Children and Adolescents With Cancer**

There are new observational studies, as well as case studies, addressing fertility preservation of children and adolescents with cancer, including the risks of radiation as well as chemotherapy.<sup>88-92</sup> Parents or guardians are often interested in information about fertility preservation on behalf of their children with cancer. Impaired future fertility is difficult for children to understand but potentially may be traumatic to them as adults. Use of established methods of fertility preservation (eg, semen cryopreservation and oocyte freezing) in postpubertal minor children requires patient assent and parental consent. Unfortunately, there are no standard modalities available for fertility preservation in prepubertal children. Current techniques are limited by the patient's sexual immaturity, and all available approaches for children are experimental. Oocyte cryopreservation has been reported in children age 13 years and older. There have been numerous reports of ovarian cryopreservation in younger children, also, but there have been no reports of live births after ovarian cortical tissue cryopreserved prepubertally and reimplanted at a later date, primarily because of the young age of the study participants.<sup>93,94</sup> Efforts to preserve fertility of children using experimental methods should be attempted only under institutional review board-approved protocols. Likewise, testicular cryopreservation has been used in young children, but there are no reports of testicular transplantation in the peer-reviewed literature.

Several studies confirm that adult survivors of pediatric cancer wish they had been given more information and options about fertility, and these survivors are often uncertain about their fertility status or feel regret about no longer having an option.<sup>95,96</sup> Parents may be uncertain about making fertility related decisions on behalf of a minor; both the American Academy of Pediatrics<sup>97</sup> and the American Society for Reproductive Medicine<sup>25</sup> offer guidance for counseling parents of children with cancer.

### **Special Fertility Preservation Considerations for Patients Receiving Targeted and Biologic Therapies**

Since the publication of the 2006 guidelines, the number of novel agents and classes of therapeutic agents has expanded significantly. The Panel acknowledges that there is little available information regarding the impact of these agents on fertility, at any level of evidence, for the vast majority of these treatment modalities. One important exception is bevacizumab, for which the US Food and Drug Administration issued a warning in October 2011, reporting that ovarian

failure occurred in 34% of women receiving a bevacizumab-containing regimen for colorectal cancer compared with 2% of women receiving the same regimen without bevacizumab. Only approximately one fifth of these women recovered ovarian function. The US Food and Drug Administration therefore recommends that oncologists “inform females of reproductive potential of the risk of ovarian failure before starting treatment with bevacizumab.”<sup>98</sup> Another specific area of concern frequently encountered by clinicians is how to counsel young patients with chronic myeloid leukemia in chronic phase who are being managed with tyrosine kinase inhibitors (TKIs) such as imatinib. Although recommendations regarding management of these patients is beyond the scope of this guideline, the Update Panel wishes to note that a number of case reports, case series, and expert reviews have been published suggesting that young men receiving TKIs probably do not confer an increased risk of pregnancy-related complications or congenital anomalies to their partners and offspring,<sup>99</sup> although these men should be counseled and strongly cautioned that there are insufficient data to provide adequate reassurance. Similar level of evidence suggests that women of reproductive capacity should not become pregnant while taking TKIs, because there is strong evidence that these agents are teratogenic in animal models.

## PROVIDER AND PATIENT COMMUNICATION

Health care providers can use the following points for a discussion of infertility and fertility preservation with a patient (or parents or guardians):

Inform patient of individual risk

- Some cancer treatments can cause infertility or early menopause.
- To determine your individual risks, we have considered your individual factors such as your cancer type, age, and treatment plan.
- Based on that information, we believe that your risk is [high, medium, low, nonexistent].
- Your fertility status before cancer may also play a role in your individual risks [discuss if relevant].

Discuss common concerns

Options

- There are many available fertility preservation and parenthood after cancer options for you to consider.
- For men, the most common and successful option is sperm banking. Other experimental options exist, if sperm banking is not a viable option for you.
- For women, the most established options are embryo and egg freezing. Other experimental options exist, if these are not viable options for you.
- A referral can be made for you to an appropriate reproductive specialist for a consultation, if you would like to learn more.

Time

- Time is of the essence. Fertility preservation treatments need to be completed before you start chemotherapy and/or irradiation.
- For men, sperm banking can be done quickly and can be done every 24 hours, as long as necessary, to collect the desired number of samples.
- For women, fertility preservation may take 2 to 4 weeks for

established techniques. However, some experimental approaches can be implemented sooner, so timely referral to a reproductive specialist is important.

Costs

- Insurance coverage for fertility preservation for patients with cancer is improving. The fertility center/sperm bank will be able to check your benefits for you.
- 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 patients worry about the safety of pregnancy after cancer. Data are limited, but there seems to be no increased risk of cancer recurrence from fertility preservation methods or pregnancy, even in hormonally sensitive tumors.
- Similarly, many patients 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 increases the risk of cancer or congenital abnormalities in the progeny.

Refer to appropriate specialists

- Reproductive specialists: For more information about fertility preservation, a referral can be provided to a local fertility specialist/sperm bank.
- Mental health professionals: Many patients find cancer treatment-related infertility distressing. There is a lot to think about in addition to cancer. You can be referred to a counselor, if that would be helpful. Many of the reproductive centers also have counselors available to discuss these issues, so you may be able to see someone while there for your consultation.
- Advocacy organizations: Many advocacy organizations such as LIVESTRONG Foundation's Fertile Hope Program and the Oncofertility Consortium also provide useful information and resources to help facilitate your decision making. They may also have financial assistance programs specifically designed to help with fertility preservation.

## HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial, ethnic, and socioeconomic disparities in health care contribute significantly to this problem in the United States. Minority racial/ethnic patients with cancer suffer disproportionately from comorbidities, can experience substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poorer quality care than other Americans.<sup>100-103</sup> Many other patients lack access to care because they live at a distance from appropriate treatment or reproductive specialty facilities.

Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest-level fertility preservation advice and treatment to these vulnerable populations. In particular, no patient should be excluded from consideration for discussion



## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Administrative support:** Alison W. Loren, Pamela B. Mangu, Kutluk Oktay

**Provision of study materials or patients:** Kutluk Oktay

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

## ADDITIONAL RESOURCES

Data Supplements and clinical tools and resources can be found at <http://www.asco.org/guidelines/fertility>. Patient information is also available at <http://www.cancer.net>.

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**Appendix****Table A1.** Fertility Preservation for Patients With Cancer Guideline Update Panel Members

Member	Affiliation/Institution
Kutluk Oktay, MD, Co-Chair	Innovation Institute for Fertility Preservation, New York Medical College, Rye and New York City, NY
Alison W. Loren, MD, Co-Chair	Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
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Ann H. Partridge, MD	Dana-Farber Cancer Institute, Boston, MA
Gwendolyn Quinn, PhD	Moffitt Cancer Center, Tampa, FL
W. Hamish Wallace, MD	Royal Hospital for Sick Children, Edinburgh, United Kingdom