FERTILITY PRESERVATION FOR PATIENTS WITH CANCER

Clinical Practice Guideline Update
Introduction

• In 2006, the American Society of Clinical Oncology (ASCO) published a clinical practice guideline on fertility preservation for adults and children with cancer

• ASCO Guidelines are updated at intervals by Update Committees of their original Expert Panels

• After review and analysis of the evidence published since the original 2006 guideline, the Update Panel concluded that new evidence was not compelling enough to warrant substantive changes to any of the 2006 guideline recommendations, but clarifications and updates were added
Guideline Methodology: Systematic Review

- Literature review focused on available publications from March 2006 through January 2013
  - MEDLINE
  - Cochrane Collaboration Library
- 222 new publications met inclusion criteria
  - Mostly observational studies, cohort studies, and case series or reports, with few randomized clinical trials

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Clinical Questions

1. Are patients with cancer interested in interventions to preserve 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 health care providers in advising patients about fertility preservation options?

Special fertility preservation considerations for children and adolescents and for patients receiving targeted and biologic therapies with cancer are addressed.
Recommendations

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.

1.2: Health care providers should refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists.
Recommendations

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 chart.
Recommendations

2.1: *Sperm cryopreservation*. Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.

2.2: *Hormonal gonadoprotection*. Hormonal therapy in men is not successful in preserving fertility. It is not recommended.

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 a part of clinical trials or approved experimental protocols.
Recommendations

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.
Recommendations

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.

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 to old protocols. Thus, oocyte harvesting for the purpose of oocyte or embryo cryopreservation is now possible on a cycle day-independent schedule.*
Recommendations

3.3: **Ovarian transposition.** Ovarian transposition (oophoropexy) can be offered when pelvic radiation 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.*
3.5: Ovarian suppression. Currently, there is insufficient evidence regarding the effectiveness of gonadotropin releasing hormone analogs (GnRHa) and other means of ovarian suppression on 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.
Recommendations

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.

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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 utilizing 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.
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.

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.
Recommendations

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 a patient is distressed about potential infertility.
Recommendations

5.1: Suggest established methods of fertility preservation (eg, semen or oocyte cryopreservation) for postpubertal minor children, with patient assent and parents or guardians consent.

For prepubertal minor children the only fertility preservation options are ovarian and testicular cryopreservation, which are investigational.
Special Fertility 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 modalities. On important exception is bevacizumab – with ovarian failure occurring more often in women receiving it, although additional studies are needed. Another area of concern is how to counsel young patients with CML in chronic phase who are being managed with tyrosine kinase inhibitors (TKIs).
Patient and Clinician 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
  • In order to determine your individual risks, we’ve 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]
Patient and Clinician Communication

- Discuss Common Concerns:
  - Options
  - Time
  - Costs
  - Risks of Pregnancy & Children After Cancer

- Refer to Appropriate Specialists:
  - Reproductive Specialists
  - Mental Health Professionals
  - Advocacy Organizations
    - LIVESTRONG; Fertile Hope; Living Beyond Breast Cancer
Health Disparities

• Racial, ethnic and socioeconomic disparities may lead to limited access to health care

• Minority racial/ethnic cancer patients:
  • Suffer disproportionately from co-morbidities
  • May experience substantial obstacles to receiving care
  • Are more likely to be uninsured
  • Are at greater risk of receiving poorer quality care
Health Disparities

• Awareness of these disparities should be considered in the context of guideline

• Discussing infertility and introducing the possibility of fertility preservation leads to improved quality of life and diminished distress in all patient populations

• No patient should be excluded from consideration for discussion of fertility preservation for any reason, including age, prognosis, socioeconomic status, or parity

• Fertility preservation should be considered and encouraged in all patients regardless of financial or insurance boundaries
The Bottom Line

• **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

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

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The Bottom Line

• **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 chart

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The Bottom Line

**Key Recommendations**

- 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
The Bottom Line

• **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 therapy
The Bottom Line

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

• **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
Additional Resources

• A Data Supplement 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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