American Society of Clinical Oncology

Making a world of difference in cancer care

Fertility Preservation in People Treated for Cancer

Clinical Practice Guideline

Introduction

- ASCO convened an Expert Panel to develop guidance for practicing oncologists about available fertility preservation methods and related issues in people treated for cancer.
- This guideline focuses on fertility preservation methods for men, women and children undergoing cancer treatment.
- The Panel agrees that any oncologist seeing fertile patients for consideration of cancer therapy should be addressing potential treatment-related infertility with them or, in the case of children, with their parents or guardians.

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Introduction (cont'd)

- Review of the fertility preservation literature reveals a paucity of large and/or randomized studies. Most data used in this guideline come from cohort studies, case series, small nonrandomized clinical trials or case reports.

- Though the guideline provides some information on the risks associated with several cancer therapies, the Panel did not attempt to review and quantify risks to fertility from various cancers and treatments.

- The focus is restricted to interventions aimed at fertility preservation; the guidelines do not address methods of fertility restoration after completion of cancer treatment nor the risks of assisted reproductive techniques except those unique to cancer patients.

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Guideline Methodology: Systematic Review

- An ASCO Expert Panel completed a review of the pertinent literature from 1987 through March 2005:
  - ✓ MEDLINE
  - ✓ PreMEDLINE
  - ✓ Cochrane Collaboration Library
  - ✓ National Cancer Institute Physician Data Query (PDQ)
  - ✓ ClinicalTrials.gov
- Literature Search Results:

Total Potential Articles	1675
Dual Independent Abstract Review	868
Full-Text Articles Reviewed	405
Total Articles (Met Inclusion and *a priori* Criteria)	276

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Guideline Methodology (cont'd): Panel Members

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• Lawrence V. Brennan, MD	Oncology/Hematology Care
• Lindsay Nohr Beck	Fertile Hope
• Ann H. Partridge, MD MPH	Dana-Farber Cancer Institute
• Pasquale Patrizio, MD MBE	Yale University Fertility Center
• Leslie R. Schover, PhD	MD Anderson Cancer Center
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Background

- Fertility preservation is often possible in people undergoing treatment for cancer.
- Infertility is functionally defined as the inability to conceive after one year of intercourse without contraception.
- The effects of chemotherapy and radiation therapy on fertility depend on the drug or size/location of the radiation field, dose, dose intensity, method of administration, disease, age, gender, and pre-treatment fertility of the patient.
- Male and female fertility may be transiently or permanently affected by cancer treatment or only become manifest later in women through premature ovarian failure.

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Background (cont'd)

- Male infertility can result from:
  - Disease
  - Anatomic problems
  - Primary or secondary hormonal insufficiency
  - Damage or depletion of the germinal stem cells.

- The measurable effects of chemotherapy or radiotherapy include compromised sperm number, motility, morphology, and DNA integrity.

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Background (cont'd)

- Female fertility can be compromised by any treatment that:
  - Decreases the number of primordial follicles
  - Affects hormonal balance
  - Interferes with the functioning of the ovaries, fallopian tubes, uterus or cervix.
- The Panel wishes to emphasize that female fertility may be compromised despite maintenance or resumption of cyclic menses.
- Even if women are initially fertile after cancer treatment, the duration of their fertility may be shortened by premature menopause.

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Guideline Questions

1. Are cancer patients 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 the oncologist in advising patients about fertility preservation options?

Are cancer patients interested in interventions to preserve fertility?

- Fertility preservation is of great importance to many people diagnosed with cancer.
- Most cancer survivors prefer to have biological offspring despite serious concerns.
- Surveys of cancer survivors have identified an increased risk of emotional distress in those who become infertile because of their treatment.
- Long-term quality of life is affected by unresolved grief and depression.
- Patients may choose a less efficacious treatment strategy in order to avoid toxicity and complications that could interfere with fertility.

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Patient Interest in Preserving Fertility (cont'd)

- **Special Considerations in Children:**
  - Impaired future fertility is difficult for children to conceptualize, but potentially traumatic to them as adults.
  - Spermarche occurs at approximately 13-14 years, but once sperm are present, the patient's age does not seem to affect quality of sperm produced.
  - Pre-pubertal boys have not yet developed gametes, and collection of semen through masturbation in adolescents may be compromised by embarrassment and issues of informed consent.

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Patient Interest in Preserving Fertility (cont'd)

- **Recommendation (Special Considerations in Children):**
  - Use of established methods of fertility preservation (semen cryopreservation and embryo freezing) in postpubertal minor children requires patient assent and parental consent.
  - The modalities that are available to prepubertal children to preserve their fertility are limited by the sexual immaturity of the children and are essentially experimental.
  - Efforts to preserve fertility of children using experimental methods should only be attempted under IRB-approved protocols where proper attainment of informed consent from a legally authorized representative(s) (i.e. parent(s) or guardian(s)) and of childhood assent can be ensured.

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What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males?

- **Options for preserving fertility in males:**
  - Sperm Cryopreservation- involves freezing and banking sperm collected through masturbation, rectal electroejacualtion, testicular aspiration or post-masturbation urine.
  - Hormonal Gonadoprotection-uses hormonal therapies to protect testicular tissue during chemotherapy or radiation therapy.
  - Other Methods-includes testicular tissue cryopreservation and testis grafting.

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Fertility Preservation in Males (cont′d)

- **Recommendation (Fertility Preservation in Males):**
  - The available evidence suggests that **sperm cryopreservation is an effective method** of fertility preservation in males treated for cancer.
  - **Hormonal gonadoprotection is ineffective** when highly sterilizing chemotherapy is given.

Fertility Preservation in Males (cont'd)

- **Recommendation (Sperm Cryopreservation):**
  - Oncologists should make every effort to discuss sperm banking with appropriate patients.
  - It is strongly recommended that sperm are collected prior to initiation of cancer therapy because the quality of the sample and sperm DNA integrity may be compromised even after a single treatment session.

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Fertility Preservation in Males (cont'd):

- **Sperm Cryopreservation**
  - Depending on type of cancer (esp. testicular cancer and Hodgkin lymphoma) **and** the overall condition of the patient sperm quality may be poor even in those who have not yet started treatment.
  - Many patients have to start chemotherapy soon enough to limit the number of ejaculates.
  - It is still reasonable to make every effort to bank sperm, since recent progress in intracytoplasmic sperm injection (ICSI) allows the successful freezing and future use of a very limited amount of sperm.

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Fertility Preservation in Males (cont'd)

- **Hormonal Gonadoprotection**
  - The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in cancer patients.
  - Hormonal therapy in men is not successful in preserving fertility when highly sterilizing chemotherapy is given.

Fertility Preservation in Males (cont'd)

- **Other Methods**

  The following methods remain experimental and have not been tested in humans:

  - Testicular tissue cryopreservation or reimplantation
  - Testis grafting with maturation in SCID mice

Please Note

The only methods of fertility preservation potentially available to prepubertal boys are the experimental methods mentioned above.

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Fertility Preservation in Males (cont′d)

- **<u>Recommendation (Other Considerations)</u>:**
  - Men should be advised of a possible, not yet quantifiable, higher risk of genetic damage in sperm stored after initiation of cancer therapy.
  - Long-term follow up of progeny is recommended.

What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?

- **Options for preserving fertility in females:**
  - Embryo Cryopreservation-harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation
  - Oocyte Cryopreservation-harvesting and freezing of unfertilized eggs
  - Ovarian Tissue Cryopreservation-freezing of ovarian tissue and reimplantation after cancer treatment
  - Ovarian Suppression-use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy
  - Ovarian Transposition-surgical repositioning of ovaries away from the radiation field
  - Conservative Gynecologic Surgery (Radical Trachelectomy) -surgical removal of the cervix while preserving the uterus

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Fertility Preservation Options in Females (cont'd)

- **Fertility preservation options in females depend on the patient's:**
  - Age
  - Type of treatment
  - Diagnosis
  - Partner status
  - Time available
  - Potential that cancer has metastasized to the ovaries

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Fertility Preservation Options in Females (cont'd)

- **<u>Recommendation (Embryo Cryopreservation)</u>:**
  - Embryo cryopreservation is considered an established fertility preservation method as it has routinely been used for storing surplus embryos after in vitro fertilization for infertility treatment.

Fertility Preservation Options in Females (cont'd)

- **Embryo Cryopreservation**
  - Requires ~2 weeks of ovarian stimulation w/daily injections of FSH from the onset of menses.
  - A delay of 2-6 weeks in chemotherapy initiation may be required if reproductive specialists do not see women early in their menstrual cycle.
  - This approach may be associated with high out-of-pocket costs for most women.
  - Long-term follow up with a larger number of patients is needed to evaluate the safety and efficacy of this approach.
  - For women with hormone-sensitive tumors, alternative hormonal stimulation approaches such as letrozole or tamoxifen have been developed to theoretically reduce the potential risk of estrogen exposure.

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Fertility Preservation Options in Females (cont'd)

- **Recommendation (Oocyte Cryopreservation):**
  - Cryopreservation of unfertilized oocytes is another option for fertility preservation particularly in patients for whom:
    - A partner is unavailable, or
    - Religious or ethical objections conflict with embryo freezing.
  - Oocyte cryopreservation should only be performed in centers with the necessary expertise, and the Panel recommends participation in IRB-approved protocols.

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Fertility Preservation Options in Females (cont′d)

- **Oocyte Cryopreservation**
  - Ovarian stimulation and harvesting requirements are identical to those of embryo cryopreservation, and thus this technique is associated with similar concerns regarding delays in therapy and potential risks of short-term exposure to high hormonal levels.
  - As with embryo cryopreservation, letrozole or tamoxifen can be used.
  - There have been approximately 120 births with this approach. Further research is needed to delineate the current success rates and safety, as well as to improve the efficiency of this procedure.

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Fertility Preservation Options in Females (cont'd)

- **<u>Recommendation (Ovarian Tissue Cryopreservation)</u>:**

  Ovarian cryopreservation and transplantation procedures should only be performed in centers with the necessary expertise under IRB-approved protocols that include follow-up for recurrent cancer.

Fertility Preservation Options in Females (cont'd)

- **Ovarian Tissue Cryopreservation**
  - Ovarian tissue is removed laparoscopically and frozen.
  - At a later date, the ovarian tissue is thawed and reimplanted.
  - This is an investigational method of fertility preservation with the advantage of requiring neither a sperm donor nor ovarian stimulation.
  - Because there are too few primordial follicles remaining, the benefit of ovarian cryopreservation for women >40 years of age is very uncertain.

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Fertility Preservation Options in Females (cont′d)

- **Ovarian Tissue Cryopreservation (cont′d)**
  - One concern with reimplanting ovarian tissue is the potential for reintroduction of cancer cells.
  - Thus, safe and reliable screening methods to detect malignant cells in ovarian tissue are necessary if this strategy is to become a standard therapy.
  - In patients with high risk of ovarian involvement, xenografting and ex vivo follicle growth are experimental but not yet practical possibilities.

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Fertility Preservation Options in Females (cont′d)

- **<u>Recommendation (Ovarian Suppression)</u>:**
  - At this time, since there is insufficient evidence regarding the safety and effectiveness of GnRH analogs and other means of ovarian suppression on female fertility preservation, women interested in ovarian suppression for this purpose are encouraged to participate in clinical trials.

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Fertility Preservation Options in Females (cont'd)

- **<u>Recommendation (Ovarian Transposition)</u>:**
  - Ovarian transposition (oophoropexy) can be offered when pelvic radiation is used for cancer treatment.
  - Because of the risk of remigration of the ovaries, this procedure should be performed as close to the radiation treatment as possible.

Fertility Preservation Options in Females (cont'd)

- **Ovarian Transposition**
  - This procedure can be done laparoscopically if laparotomy is not needed for the primary treatment of the tumor.
  - Because of the risk of remigration of the ovaries, this procedure should be performed as close to the radiation treatment as possible.
  - The overall success rate as judged by preservation of short-term menstrual function is approximately 50%. Scatter radiation and alteration of ovarian blood supply appear to be the main reasons behind the failures.
  - If infertility develops and in vitro fertilization is needed after ovarian transposition, however, the performance of oocyte retrieval becomes more complicated.

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Fertility Preservation Options in Females (cont'd)

- **Conservative Gynecologic Surgery**
  - In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery and/or lower dose chemotherapy.
  - Nearly 50% of women diagnosed with cervical carcinoma under the age of 40 are eligible for radical trachelectomy.
  - It has been suggested that this procedure be restricted to stage 1A2-IB disease with <2 cm in diameter with <10 mm invasion.

Fertility Preservation Options in Females (cont'd)

- **Conservative Gynecologic Surgery (cont'd)**
  - The recurrence rates following radical trachelectomy appear to be similar to that of radical hysterectomy but no randomized study exists.
  - About 230 women underwent the procedure with over 60 live births resulting.
  - There is an increased risk in midtrimester losses and preterm birth.
  - There is also a higher incidence of infertility due to cervical abnormalities, which would require the use of assisted reproduction technologies.

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Fertility Preservation Options in Females (cont'd)

- **Other Considerations**
  - Of special concern in breast and gynecologic malignancies is the possibility that fertility preservation interventions and subsequent pregnancy may increase the risk of cancer recurrence.
  - While several case control and retrospective cohort studies have not shown a decrement in survival or an increase in risk of recurrence with pregnancy, the studies are all limited by significant biases, and concerns remain for some women and their physicians.

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What is the role of the oncologist in advising patients about fertility preservation options?

1. **Discuss** infertility as a potential risk of therapy.
2. **Answer basic questions** about whether fertility preservation options decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring.
3. **Refer** patients to reproductive specialists and psychosocial providers.

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Advising Patients About Fertility Preservation (cont'd)

- **<u>Recommendation (Discussing Infertility)</u>:**

  As with the other potential complications of cancer treatment, oncologists have a responsibility to inform patients about the risks that their cancer treatment will permanently impair fertility.

A physician's recommendation is almost as influential as the patient's desire for children in the future.

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Advising Patients About Fertility Preservation (cont'd)

- **Reasons oncologists may not discuss infertility:**
  1. Insufficient time due to need to prioritize discussion about immediate or potentially life-threatening complications.
  2. Data regarding the risks of infertility with various chemotherapy regimens are poor or nonexistent.
  3. The importance of fertility to cancer survivors is not recognized.
  4. Belief that the cost of fertility preservation interventions is prohibitive.
  5. Patient's cancer prognosis is poor.
  6. Belief that patients would not be interested for other reasons.
  7. Emotional discomfort with discussing fertility issues.

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Advising Patients About Fertility Preservation (cont'd)

Points of Discussion Between the Patient and Physician

1. Cancer and cancer treatments vary in their likelihood of causing infertility.
2. Consider preservation options early to maximize the likelihood of success.
3. Sperm cryopreservation and embryo freezing are the methods of fertility preservation with the highest likelihood of success.
4. There appears to be no detectable increased risk of disease recurrence associated with most fertility preservation methods and pregnancy.
5. Aside from hereditary genetic syndromes and in-utero exposure to chemotherapy, 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.
6. Treatment-related infertility may be associated with psychosocial distress.

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Advising Patients About Fertility Preservation (cont'd)

- **Recommendations (Answering Basic Questions):**

  At present, there does not appear to be a clear detrimental effect from any of the available fertility sparing interventions. However, patients should be encouraged to participate in registries and clinical studies as available to define further the safety of fertility preservation interventions and strategies.

  Short and long-term follow-up following fertility sparing interventions for women with cancer is warranted. At the present time, in light of concerns, women with a history of cancer and cancer treatment should be considered high risk for perinatal complications and would be prudent to seek specialized perinatal care.

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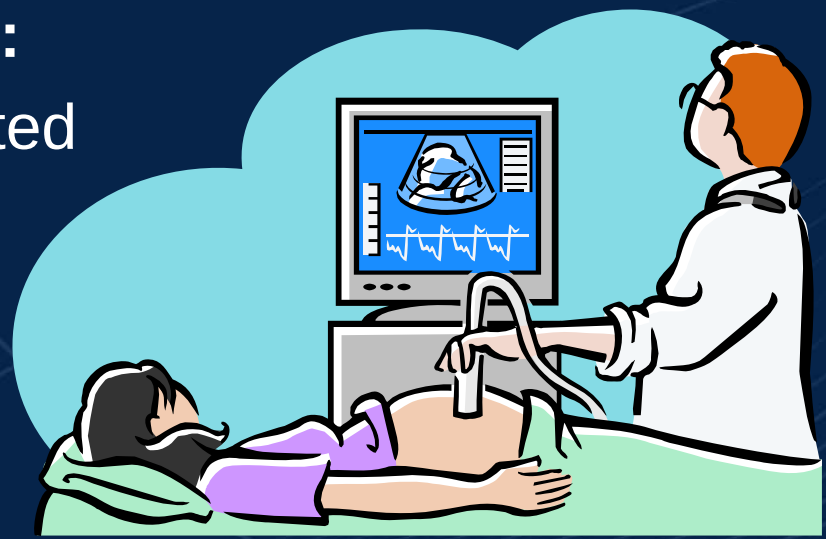
Advising Patients About Fertility Preservation (cont'd)

- **Recommendation (Answering Basic Questions, cont'd):**
- Patients should be encouraged to participate in registries and clinical studies as available to define further the safety of fertility preservation interventions and strategies.

- **Recommendation (Referral):**

Oncologists should refer interested and appropriate patients to reproductive specialists.



Advising Patients About Fertility Preservation (cont'd)

- When referring patients, oncologists should remember that many methods are still investigational.
- The experience of the infertility specialist in working with cancer patients should also be considered.
- One option the oncologist should routinely offer is a referral for psychological counseling when a man or woman has moderate to severe distress about potential infertility.

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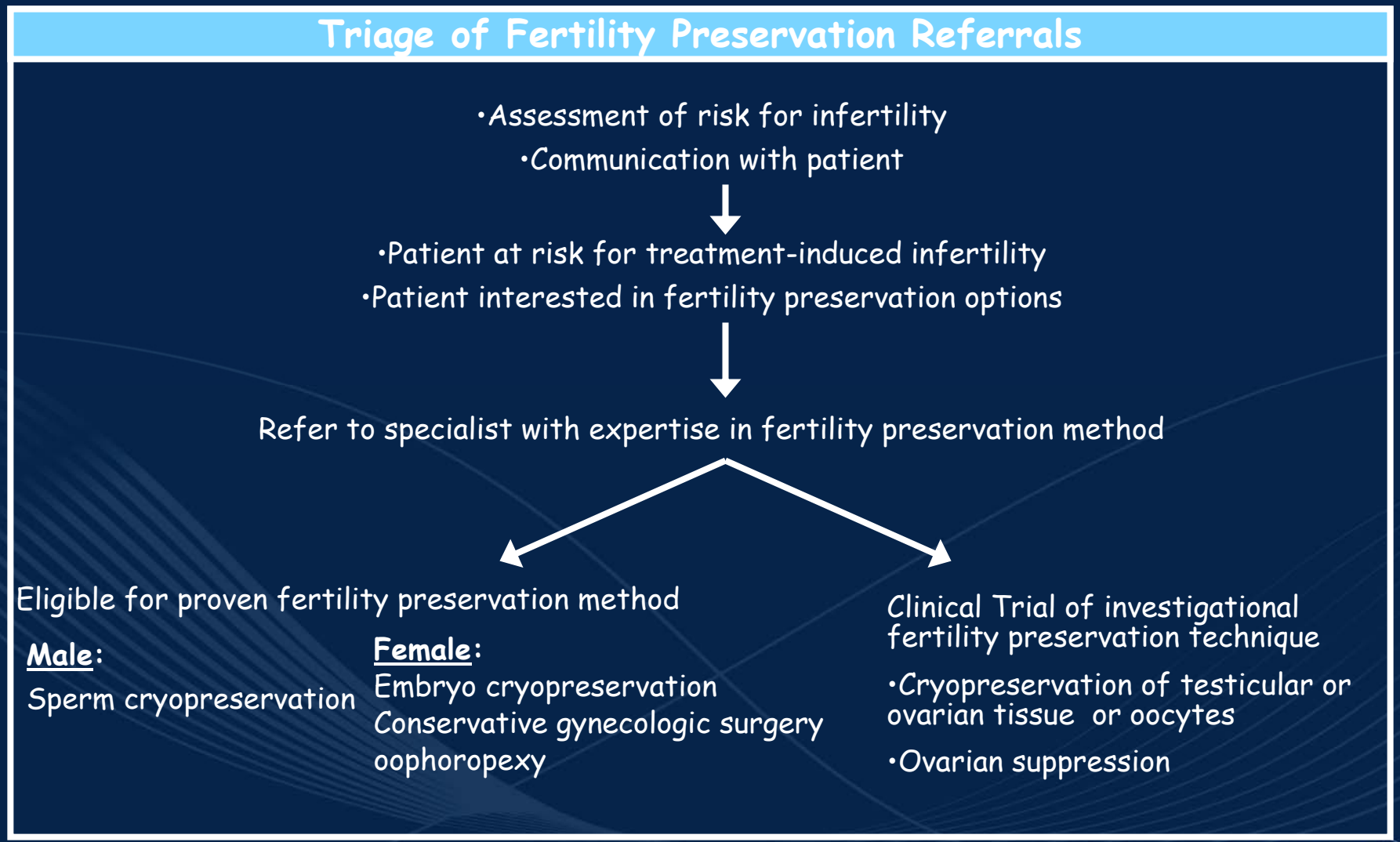
Triage of Fertility Preservation Referrals



Summary of Fertility Preservation Options in Males

Intervention	Definition	Comment	Considerations
Sperm cryopreservation after masturbation	Freezing sperm obtained through masturbation	The most established technique for fertility preservation in men; large cohort studies in men with cancer	Outpatient procedure
Sperm cryopreservation after alternative methods of sperm collection	Freezing sperm obtained through rectal electroejaculation under sedation, testicular aspiration or extraction, or from a post-masturbation urine sample.	Small case series and case reports	Testicular sperm extraction – outpatient surgical procedure
Gonadal shielding during radiation therapy	Use of shielding to reduce the dose of radiation delivered to the testicles	Case series	
Testicular tissue cryopreservation Testis xenografting Spermatogonial isolation	Freezing testicular tissue or germ cells and reimplantation after cancer treatment or maturation in animals	Has not been tested in humans; successful application in animal models	Outpatient surgical procedure
Testicular suppression with Gonadotropin Releasing Hormone (GnRH) analogs or antagonists	Use of hormonal therapies to protect testicular tissue during chemotherapy or radiation therapy	Studies do not support the effectiveness of this approach	

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Summary of Fertility Preservation Options in Females

Intervention	Definition	Comment	Considerations
Embryo cryopreservation	Harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation	The most established technique for fertility preservation in women.	-Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle. -Outpatient surgical procedure -Requires partner or donor sperm
Oocyte Cryopreservation	Harvesting and freezing of unfertilized eggs	Small case series and case reports; as of 2005, 120 live births reported, approximately 1.6% live births per frozen oocyte (3-4 times lower than standard IVF)	-Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle. -Outpatient surgical procedure
Ovarian Cryopreservation and Transplantation	Freezing of ovarian tissue and reimplantation after cancer treatment	Case reports; as of 2005, 2 live births reported	-Not suitable when risk of ovarian involvement is high. -Same day outpatient surgical procedure
Gonadal shielding during radiation therapy	Use of shielding to reduce the dose of radiation delivered to the reproductive organs	Case series	

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Summary of Fertility Preservation Options in Females (cont'd)

Intervention	Definition	Comment	Considerations
Ovarian Transposition (oophoropexy)	Surgical repositioning of ovaries away from the radiation field	Large cohort studies and case series suggest approximately 50% chance of success due to altered ovarian blood flow and scattered radiation	-Same day outpatient surgical procedure -Transposition should be performed just before radiation therapy to prevent return of ovaries to former position. -May need repositioning or in vitro fertilization (IVF) to conceive.
Trachelectomy	Surgical removal of the cervix while preserving the uterus	Large case series and case reports	-Inpatient surgical procedure -Limited to early stage cervical cancer; no evidence of higher cancer relapse rate in appropriate candidates -Expertise may not be widely available
Ovarian suppression with Gonadotropin Releasing Hormone (GnRH) analogs or antagonists	Use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy	Small randomized studies and case series. Larger randomized trials in progress.	-Medication given before and during treatment with chemotherapy

Conclusions

- Fertility preservation is often possible in people undergoing cancer treatment.
- Broader application of fertility preservation methods is limited by several factors:
  - Lack of knowledge about the risk of infertility with current cancer treatments,
  - Failure to discuss and consider options prior to treatment,
  - Lack of insurance coverage for most procedures with consequent high out of pocket costs,
  - Investigational status of many fertility preservation methods.
- To preserve the full range of options, fertility preservation approaches should be considered early during treatment planning.

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Conclusions (cont'd)

- Fertility preservation methods are still applied relatively infrequently in the cancer population, limiting greater knowledge about success and effects of different potential interventions.
- People attempting fertility preservation in the context of cancer treatment are encouraged to enroll in clinical trials that will advance the state of knowledge.
- Except for sperm cryopreservation and embryo freezing, most of the available fertility preservation methods should be considered investigational and be performed in centers with the necessary expertise.
- As part of education and informed consent prior to cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists.

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Resources for Patients

- Cancer/Fertility Related Patient Advocacy
  - Fertile Hope (http://www.fertilehope.org)
  - Lance Armstrong Foundation/Livestrong (http://www.livestrong.org)

ASCO Resources

- This slide set and the full text ASCO guideline on fertility preservation are located at:
  http://www.asco.org/guidelines/fertility
- A patient guide is posted at http://www.cancer.net

ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

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