CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Guideline for Fertility Preservation for Patients with Cancer

COG Supportive Care Endorsed Guidelines

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The "Fertility Preservation for Patients with Cancer" guideline was endorsed by the COG Supportive Care Guideline Committee in December 2014. The entire document and implementation tools provided by the guideline developers are available at:
http://www.instituteforquality.org/fertility-preservation-patients-cancer-american-society-clinical-oncology-guideline-update

A summary is published in the Journal of Clinical Oncology 2013; 31:2500-2510. http://jco.ascopubs.org/content/31/19/2500

The purpose of this guideline is to address four 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 the oncologist in advising patients about fertility preservation options? Special fertility preservation considerations for children and adolescents with cancer are also provided.

The recommendations pertaining to questions 2 and 3 and pediatric considerations are provided here. Please refer to the source document for recommendations pertaining to questions 1 and 4.

Summary of Recommendations for Fertility Preservation for Patients with Cancer

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males?	
2.1 Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with post-pubertal males receiving cancer treatment.	**No formal grading system used**
2.2 Hormonal gonado-protection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.	**No formal grading system used**
2.3 Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and re-implantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols.	**No formal grading system used**
2.4 Post-chemotherapy: 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. Intra-cytoplasmic sperm injection allows the future use of a very limited amount of sperm; thus, even in these compromised scenarios, fertility may still be preserved.	**No formal grading system used**

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
3. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?	
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.	**No formal grading system used**
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.	**No formal grading system used**
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.	**No formal grading system used**
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 < 2 cm and invasion < 10mm. 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.	**No formal grading system used**

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
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.	**No formal grading system used**
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 re-implanting 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.	**No formal grading system used**
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.	**No formal grading system used**
5. Special fertility preservation considerations for children and adolescents with cancer:	
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.	**No formal grading system used**

Appendix 1: GRADE

Strength of Recommendations:

Strong Recommendation	When using GRADE, panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Strength of Recommendations Determinants:

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Quality of Evidence

High Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	Any estimate of effect is very uncertain

Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ, 2008; 336: 924-926.
Guyatt, G.H., et al., *GRADE: going from evidence to recommendations.* BMJ, 2008; 336: 1049-1051.