Chapter 17

Oncofertility Consortium Consensus Statement: Guidelines for Ovarian Tissue Cryopreservation

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In vitro fertilization (IVF) and storage of the resulting embryos is currently a proven method of fertility preservation for women who face an immediate threat to their future fertility. This method, however, is suitable for a fraction of patients and depends on a number of factors that may include her diagnosis, age, partner status, willingness to accept donor sperm, desire to freeze embryos, and ability to pay for these services. As fertility preservation techniques evolve, it is critical that physicians continue to evaluate practice guidelines in order to offer a wider menu of fertility preservation options tailored to each patient's specific clinical scenario, to the risk-benefit ratio and takes into consideration the patient's values.

Practice guidelines and consensus statements for fertility preservation for oncology patients reflect the current evidence based and ethical practices in the related disciplines of oncology and reproductive endocrinology. Both the American Society of Clinical Oncology (ASCO) and the American Society of Reproductive Medicine (ASRM) recently published guidelines to describe the circumstances under which fertility preservation should be discussed and to describe patients for which experimental methods, such as ovarian cryopreservation, may be suitable [1–3]. Taken together, these documents are comprehensive in their description of:

1. The need for discussion with patients about impaired fertility resulting from cancer treatment,
2. The need for early referral to a reproductive specialist to improve fertility outcome and minimize the delay of cancer treatment,
3. Malignant and benign conditions that render a patient a potential candidate for IRB approved protocols for ovarian cryopreservation.
4. The current established and experimental options available to preserve female fertility, and
5. The difficulty in providing and accurate estimate of the degree of future impaired fertility.

International interdisciplinary committees have also produced consensus statements to describe practice guidelines for offering experimental fertility preservation options to patients. Although both domestic and foreign guidelines illustrate the importance of offering fertility preservation to cancer patients, the interpretation of these guidelines that influences clinical practice may ultimately reflect the clinician's bias of "good candidates" for experimental options based on his or her experience, values, or availability of resources. Researchers in the United Kingdom have offered distilled interpretations of the interdisciplinary committee guidelines for candidates for ovarian cryopreservation [4], which suggests that clinicians would appreciate a relatively short "list" of criteria to consult prior to referring or offering ovarian tissue cryopreservation (see Fig. 17.1).

We find, however, the Edinburgh guidelines are inconsistent with criteria that would be used to offer reproductive assistance to patients in the United States. We propose new criteria for candidates for ovarian tissue cryopreservation that is consistent with the ASCO and ASRM consensus statements [1–3]. These guidelines could be used to identify potential candidates for ovarian cryopreservation in cases where a woman is at risk for iatrogenic infertility as a result of surgical or medical treatment for a benign or malignant condition. Due to the experimental nature of ovarian cryopreservation, in vitro maturation of follicles, and ovarian transplantation, these recommendations are not currently applicable for patients who desire fertility preservation in the absence of an immediate or iatrogenic threat.

Proposed criteria for candidate selection

1. Age <42 years
2. Cannot or chooses not to undergo an IVF cycle, regardless of partner status
3. Demonstrated or assumed pre-menopausal ovarian function
4. Risk of significant acceleration of anticipated loss of ovarian function
5. Informed consent from adult patient
6. Informed assent from patients <18 years, and informed parental/guardian consent
7. Meets criteria to be an appropriate candidate for an elective surgical procedure
8. Would consider having a child in the future
9. In the case of hormone-sensitive malignancy in which ovarian stimulation or oocyte retrieval are contraindicated.

Edinburgh Criteria for Selection for Ovarian Cryopreservation

1. Age <30
2. No previous chemotherapy or radiotherapy (patients <15 considered with previous low risk chemotherapy)
3. Realistic chance of long-term survival
4. High risk of treatment induced immediate ovarian failure (estimated at >50%)
5. Informed consent from patient or (in the case of and incompetent child) from parents
6. Negative HIV and hepatitis serology
7. No existing children

Fig. 17.1 Edinburgh criteria for selection of candidates for ovarian cryopreservation. Criteria are based on multidisciplinary discussion and working group report of the Royal College of Obstetricians and Gynaecologists [4]

The above criteria uses the age and testing of the potential reproductive status of the woman to be consistent with the criteria that would be used to identify the patient as a candidate for IVF if her ovary were to remain in situ. If time constraints prohibit testing at the appropriate time in her cycle, it should be assumed the patient is currently fertile in the absence of evidence to the contrary. After the process of informed consent, patients have the right to refuse to delay their own cancer treatment in service of IVF or to decide this method is not acceptable to them. Patients should be extensively counseled that IVF and embryo cryopreservation is an established method of fertility preservation and that ovarian cryopreservation is experimental, however counseling patients concurrently about IVF, oocyte cryopreservation, and ovarian tissue cryopreservation would eliminate the risk that a patient would choose IVF because she did not know about other options.

Any patient who is at risk of accelerated ovarian failure significantly earlier than the norm for the population as a result of her treatment should be counseled about this risk and offered fertility preservation. Although the patient may not undergo immediate ovarian failure, a shift in her reproductive life span such that her ability to have her own genetic children may end by her early 30s instead of her early 40s is a significant factor that could significantly change her range of choices and quality of life. Current infertility practice allows healthy women to receive donor eggs up to their early 50s, thus a woman who is 40 today may still be able to use her own gametes in the future. The patient's estimated long-term survival should not be applied as a criterion since this is often difficult to predict, and cancer survivors may elect to have children in the future. Ethical analysis has not yielded arguments to use length of survival of parents or risk of recurrence as a criterion to restrict access to fertility preservation [5].

Informed consent of both adult and pediatric patients must be in compliance with the institutions IRB protocols. A minor who is able to understand the procedure presented must give her assent. The procedure cannot be done with parental consent alone. If the patient is too young to give assent, then the procedure cannot pose more than minimal risk to the patient and the benefit must be clear. In the case of both adults and children, the surgery cannot pose additional significant risk to the patient in the judgment of the health care team, and the risks are clearly explained to the patient in the consent process. Patients should meet the same criteria for fertility preserving surgery that they would need to meet for other elective surgical procedures of roughly equivalent invasiveness and duration.

The discussion of fertility preservation for the patient with hormone-sensitive malignancy is controversial – it not a clear-cut issue and there are conflicting opinions. Breast cancer is a classic model of a hormone-dependent malignancy. Some experts believe that women with breast cancer should not be offered embryo or oocyte cryopreservation prior to chemotherapy. Since the drugs used for ovulation induction as part of IVF treatment increase the levels of endogenous gonadal hormones to a supraphysiological level, concerns have arisen regarding, at least theoretically, the potential for stimulation of malignant cell growth in a patient with a hormonally sensitive tumor. Therefore, some oncologists do not recommend traditional ovarian stimulation regimens because the markedly elevated, albeit transient, levels of estrogen can induce breast cancer cell proliferation and dissemination. Instead, oocyte retrieval and embryo freezing can be performed during unstimulated (natural) cycles in these patients, however the embryo yield is often quite low. Researchers are exploring the use of selective estrogen receptor modulators, such as tamoxifen, and aromatase inhibitors, such as letrozole, to offset the brief hyperestrogenemia resulting from ovulation induction [6–8]. While these studies report modest results, the small sample sizes and short-term results warrant further investigation before broadly implementing these strategies. For patients with hormonesensitive malignancies, the reproductive endocrinologist must work in collaboration with the medical oncologist to ensure that he/she is comfortable with the brief period of hyperestrogenemia. While the debate on the use of ovulation induction therapy in breast cancer patients evolves, the option for ovarian tissue cryopreservation remains. The option of tissue cryopreservation may be ideal for these patients as it provides the opportunity for future fertility without the potential additional risks of an elevated serum hormonal milieu, which may exacerbate their existing malignancy.

The prognosis of the patient as well as HIV and Hepatitis serologies has been omitted from the guidelines. Any survivor may decide to reproduce, and length of survival after bearing children has not yielded and ethical argument against allowing survivors to reproduce. Although we acknowledge that individual practitioners may choose not to provide reproductive services to HIV positive or hepatitis positive patients, these conditions should not exclude a patient from being offered fertility preservation. In addition, adults may designate a person or persons who will have access to the stored gametes in the event of the patient's death. These individuals cannot, in turn, assign custody to somebody else not included on the list of custodians since there would be no evidence of such intent of the deceased.

Having living children does not exclude a patient from fertility treatment in the U.S. and thus should not be used as a criterion to exclude cancer patients from fertility preserving treatment. The patient need only indicate that she would consider having children in the future. Although previous chemotherapy or radiation treatment could decrease the success of either emergency IVF or the ability to mature follicles from cryopreserved tissue, these are not used as an exclusion criterion for ovarian cryopreservation. Patients should be counseled that the chance of successful pregnancy could be reduced, but the effect of decreased ovarian reserve on in vitro maturation and fertilization of cryopreserved follicles is not known at this time. Unless the patient has demonstrated ovarian failure, it should be assumed that she has adequate ovarian reserve to attempt ovarian cryopreservation regardless of age or previous treatment regimes until there is data to suggest circumstances under which in vitro maturation and fertilization of these follicles will not be successful.

The purpose of this document is to help physicians identify patients who may be good candidates for ovarian cryopreservation for fertility preservation. Patients should be counseled about the risks, benefits, and limitations of ovarian cryopreservation and embryo cryopreservation. Embryo cryopreservation is an established method, but is not suitable for all patients. Ovarian cryopreservation may be an appropriate alternative for patients who are unable to or choose not to undergo ovarian stimulation and IVF prior to a fertility-threatening treatment. When discussing alternative options such as ovarian cryopreservation, the limitations and experimental nature must be made clear so that the patient is not given false hope about the future success of the method. Patients who meet the above criteria, however, should be made aware of both established and experimental options so that they can choose the method that has the risks and benefits that best suits their medical needs and personal values.

References

1. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril 2005;83:1622–1628.
2. Practice Committee of the American Society for Reproductive Medicine and the Committee of the Society for Assisted Reproductive Technology. Ovarian tissue and oocyte cryopreservation. Fertil Steril 2006;86:S142–S147.
3. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations of fertility preservation in cancer patients. J Clin Oncol 2006;24:2917–2931.
4. Wallace WHB, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol. 2005;4:209–218.
5. Robertson JA. Cancer and fertility: ethical and legal challenges. J Natl Cancer Inst Monogr 2005;34:104–106.
6. Oktay K, Buyuk E, Davis O, et al. Fertility preservation in breast cancer patients: IVF and embryo cryopreservation after ovarian stimulation with tamoxifen. Hum Reprod 2003;18:90–95.

7. Oktay, K. Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. J Clin Oncol 2005;23:3858–3859.
8. Oktay K, Buyuk E, Libertella N, et al. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol 2005;23:4347–4353.