Chapter 31

Counseling and Consenting Women with Cancer on Their Oncofertility Options: A Clinical Perspective

Emily S. Jungheim, Kenneth R. Carson, and Douglas Brown
E.S. Jungheim (B) Department of Reproductive Endocrinology and Infertility, Barnes-Jewish Hospital, Washington University School of Medicine, St. Louis, MO, USA e-mail: emily_jungheim@yahoo.com

T.K. Woodruff et al. (eds.), *Oncofertility*, Cancer Treatment and Research 156, 403 DOI 10.1007/978-1-4419-6518-9_31

http://www.springerlink.com/content/978-1-4419-6517-2#section=759973&page=1

Introduction

The Challenges of Counseling Oncofertility Patients

Over the past decade, professional and lay organizations have raised awareness of the damaging effects some cancer treatments can have on the fertility of young women. Despite this progress, counseling and consenting cancer patients about their fertility remains complicated. Literature from the American Society for Clinical Oncology [1] (ASCO) outlines treatment regimens that may affect fertility; however, these regimens continue to evolve, making it difficult to predict how an individual's fertility may be compromised. After fertility counseling, some women elect to preserve gametes or embryos prior to cancer treatment, but doing so does not guarantee future fertility. There are risks involved with the procedures involved in acquiring these reproductive tissues. Furthermore, patients who elect gamete or embryo banking need to be counseled about additional challenges they may face – challenges predicted by the unique history of reproductive medicine.

This chapter details considerations and references we have found helpful in counseling and consenting cancer patients regarding their oncofertility options.

The Oncofertility Patient–Clinician Dialogue

Risks of Cancer Care to a Woman's Future Fertility

Ideally, a cancer patient's physician initiates discussion about fertility preservation options soon after she receives her diagnosis and certainly before she begins treatment. Unfortunately, initiating the discussion is often the most difficult step in the oncofertility dialogue. Oncologists may be aware of the threat chemotherapy poses to fertility in general terms, but unprepared to address this threat in specific cases. To help guide oncologists and other clinicians in these discussions, ASCO released recommendations on fertility preservation for cancer patients [1]. This document was created in 2006 by a multidisciplinary group of professionals including oncologists and reproductive medicine specialists. The authors of these recommendations emphasize that "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" (p. 2917). They acknowledge, however, that data regarding infertility risks associated with common chemotherapeutic regimens in women "are poor and heterogeneous" (p. 2918) and based on surrogate markers of infertility such as amenorrhea.

Table 31.1, adapted from the ASCO recommendations [1], identifies several cancer therapies that are known to almost universally result in sterilization in women. These therapies include conditioning regimens for stem cell transplantation and pelvic external beam radiation. More complicated is assessing the risks of treatment regimens associated with breast cancer treatment on fertility. There are many factors to consider including: dose and combination of agents, patient age at the time cancer treatment begins and ends, duration of treatment (e.g., endocrine therapy with tamoxifen for 5 years), baseline ovarian reserve, and pre-existing infertility. Patient variation in polymorphisms for drug metabolizing enzymes may also be important in determining a drug's effects on ovarian function; research in this area is ongoing [2]. New therapeutic agents are continually being introduced for clinical use with little knowledge of long-term sequelae. Thus, when counseling women with

Table 31.1 Risk of permanent amenorrhea after chemotherapy and radiotherapy. Adapted from Lee et al. [1]

Degree of risk	Treatment
High risk (>80%)	• Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan • External beam radiation to a field that includes the ovaries • CMF, CEF, CAF × 6 cycles in women age 40 and older
Intermediate risk	• CMF, CEF, CAF × 6 cycles in women age 30–39 • AC × 4 in women age 40 and older
Lower risk (<20%)	• CHOP × 4–6 cycles • CVP • AML therapy (anthracycline/cytarabine) • ALL therapy (multi-agent) • CMF, CEF, CAF × 6 cycles in women age less than 30
Very low or no risk	• Vincristine • Methotrexate • 5-Fluorouracil
Unknown effects	• Taxanes • Oxaliplatin • Irinotecan • Monoclonal antibodies • Tyrosine kinase inhibitors

cancer regarding their risk of treatment-related infertility, it is important not to focus only on her initial cancer diagnosis, but also on her treatment plan and baseline risk factors for infertility. In many cases, the preferred mechanism for this discussion is referral of interested patients to a fertility specialist.

Tracking fertility outcomes after specific treatment regimens in individuals is an important objective in the field of oncofertility. Until better data are available, clinicians need to be cautious when using the limited and incomplete information currently available. After counseling patients about their risks and the flaws in our existing data, it

is important for clinicians to offer patients options for dealing with these risks. Referring patients to websites such as those established by the Lance Armstrong Foundation may be helpful, but it is more appropriate to offer interested patients further discussion or referral to someone with expertise in reproductive medicine and assisted reproductive technologies (ART) and more specifically in the management of oncofertility patients.

Initiating the Discussion of Oncofertility Options

Since effective treatment of the underlying malignancy remains the driving factor in decisions about oncofertility, coordination and communication between the reproductive medicine team and the oncology team are critical. While the oncology team may initiate oncofertility discussion or referral to the reproductive medicine specialist, the primary burden of this ongoing communication usually rests with the reproductive medicine specialist. Collaboration and interaction between these two teams is key to treating patients in a timely fashion and to ensuring that patients receive consistent information regarding the most appropriate intervention given their situation.

The oncofertility treatment options we focus on in this chapter require the use of assisted reproductive technologies (ART) such as embryo banking, oocyte banking, and ovarian tissue banking. Cryopreservation of excess embryos after in vitro fertilization is an established tool in ART. Oocyte banking and ovarian tissue banking are considered experimental and should only be offered or practiced as part of a research protocol under the direction, input, and approval of the appropriate institutional review board [3–5]. Other oncofertility options include ovarian transposition and ovarian suppression with gonadotropin releasing hormone (GnRH) agonists and antagonists. Ovarian transposition has been proven to aid in protecting ovarian function against the harmful effects of pelvic irradiation and can be performed by physicians with appropriate surgical training. Although not proven, some data suggest that GnRH agonists and antagonists may be helpful for women being treated for some types of cancer. Administration of these agents does not require any specialized training.

Established Oncofertility Options for Women: Embryo Banking

Embryo banking prior to cancer treatment has risks that can be predicted from years of experience with embryo cryopreservation in the practice of ART for routine indications. Traditionally, embryo cryopreservation has been used as a means to increase the cumulative live birth rate after in vitro fertilization (IVF) in patients being treated for infertility. Typical IVF treatment begins with gonadotropin stimulation to promote ovarian follicular recruitment. Oocytes are retrieved and fertilized in vitro. The embryos are cultured for a number of days and the best quality embryos are typically transferred, leaving excess embryos to be frozen for future use. With embryo banking, all of the embryos are typically frozen soon after fertilization with little information regarding the embryos' quality.

Embryo banking can take anywhere from 2 to 6 weeks, which may limit the utility of this technique in oncofertility patients with aggressive cancer. Also, because oocytes must be

fertilized, we recommend this strategy for patients who have consenting male partners and for women without male partners who are appropriately counseled regarding the use of donor sperm [6]. For women without a partner or who do not want their oocytes to be fertilized, oocyte banking or ovarian tissue cryopreservation may be more appropriate.

While embryo banking may increase the chances a woman will have a genetically related child in the future, there are risks. Many of these risks are outlined in ASRM's guideline titled "Elements to Be Considered in Obtaining Informed Consent for ART" [7], including the risks of adverse reactions to medications, risks associated with oocyte retrieval, and risks that a patient may not respond to medication or have poor oocyte recovery rate. Several additional considerations important to discuss with patients undergoing embryo banking as part of an oncofertility strategy are delineated in ASRM's Ethics Committee statement titled "Fertility Preservation and Reproduction in Cancer Patients" [8]. The most clinically significant of these additional considerations are highlighted below along with others we have found to be important.

Success of Embryo Cryopreservation: Evidence from the Society for Assisted Reproductive Technology (SART)

As part of the counseling process, we recommend that clinicians discuss success data from the Society for Assisted Reproductive Technology (SART). SART was established in 1985, 7 years after the first IVF baby was born and 2 years after the first baby was born by a frozen embryo transfer (FET). SART publishes success data from more than 85% of ART clinics in the United States practicing in vitro fertilization. Although SART data are not specific to women with cancer undergoing embryo banking, in our practice we routinely refer to SART data (Table 31.2) when counseling cancer patients about their chances of having a live birth after IVF with FET. These data demonstrate that fresh embryos from non-donor oocytes provide better pregnancy rates than frozen embryos. However, with embryo banking, no embryos are transferred in a fresh cycle, potentially leaving better quality embryos for FET. This may lead to higher pregnancy rates than what are seen with traditional FET, but it is important to emphasize that the chances of pregnancy will never be 100%, and they are not likely to be higher than what is seen with fresh embryos.

Table 31.2 Chances of live birth and multifetal pregnancies in patients included in 2007 data from the Society for Assisted Reproductive Technology [9]

Type of ART cycle	Patient age				
IVF cycles using fresh embryos from non-donor oocytes	<35	35–37	38–40	41–42	43–44
Number of cycles	38,372	21,707	19,099	8,865	5,749
Percentage of cycles resulting in live births	39.9	30.5	21.0	11.7	4.6
Average number of embryos transferred	2.2	2.5	2.8	3.1	3.2
Percentage of live births with twins	32.9	28.4	22.0	14.9	9.1
Percentage of live births with triplets or more	1.8	2.0	1.5	0.7	0.4
Thawed embryos from non-donor oocytes	<35	35–37	38–40	41–42	43–44
Number of transfers	9,499	4,895	3,240	1,043	652
Percentage of transfers resulting in live births	34.0	30.4	25.0	20.7	14.6
Average number of embryos transferred	2.2	2.2	2.3	2.6	2.5

Unknowns of Embryo Banking for Women with Cancer: Evidence from Embryo Cryopreservation Literature

The SART data demonstrate that although embryo cryopreservation is a proven technology, it is not a guarantee for future fertility. While the techniques used for embryo banking are the same as those used for traditional embryo cryopreservation after IVF, it is important for patients to know there are no existing data specific to the success of embryo banking strategies regarding pregnancy outcomes or regarding safety in women with cancer [10, 11]. Under standard ovarian stimulation protocols, estradiol levels can reach 4,000–5,000 pg/ml unless anti-estrogen medications such as letrozole are used to keep them lower. To date, there is only one published study tracking women with breast cancer who elect ovarian stimulation using a letrozole containing protocol that shows no increased risk in cancer progression [11]. There are no data on the safety of stimulation protocols without letrozole.

Fully informed patients also need to know that specific embryo transfer practices after embryo banking have not been established. Therefore, clinicians often are guided in their transfer strategies by the ASRM embryo transfer guidelines [12]. The risk of multifetal pregnancy is higher with standard embryo transfer guidelines than it is with natural conception (Table 31.2). When to discuss the risks of multiples and the number of embryos to transfer with these patients are questions that have not been answered. Experience from the traditional IVF population would suggest that the earlier the discussion begins the better the results [13]. Further tracking of patients undergoing embryo banking as a fertility preservation option will provide insight to these unknowns.

When creating and freezing embryos for a cancer patient's future use, unforeseen conflicts may arise [14]. Potential areas of conflict that should be addressed in counseling patients include use of donor sperm [6], disposition of unused embryos [15], and disposition of embryos when relationships change (including divorce or death) [14]. Some of these conflicts are predictable as demonstrated by literature from

medicine's past. Reference to this literature may be helpful in counseling cancer patients [6, 15, 16]. Whether or not these conflicts require answers prior to proceeding with embryo banking is debatable. For legal purposes, documentation of discussions and decisions may be helpful should conflicts arise [14]. Two final explanations patients undergoing embryo banking should receive are that there does not appear to be any increased risk of congenital anomalies to children born from frozen embryos and that length of storage does not appear to be a factor in survival of embryos. However, very little data are available regarding ART offspring. Future studies tracking outcomes of ART offspring are necessary.

Experimental Oncofertility Treatments: Oocyte Cryopreservation

For women without a partner or for whom donor sperm is not an option, oocyte banking may be a suitable oncofertility option. Similar to embryo banking, oocyte banking requires ovarian stimulation with gonadotropins and oocyte retrieval. Oocytes are then cryopreserved. As with embryo banking, the entire process can take from 2 to 6 weeks depending on where the patient is in her menstrual cycle when she begins stimulation treatment. Unlike embryo banking, however, oocyte banking for future fertility is considered experimental, defined by ASRM as an infertility treatment that lacks "adequate scientific evidence of safety and efficacy" from appropriately designed, peer-reviewed published studies by different investigator groups [5, 17]. Despite this status, recent data from Italy, where laws prohibit embryo banking, suggest thawed oocytes can be successful and safe in helping patients achieve a live birth [18]. Both ASRM and the American College of Obstetricians and Gynecologists endorse the promise this technique holds for cancer patients [4, 5]. Until the practice is refined, however, oocyte banking should only be performed in the context of a clinical trial and as research under the guidance of an institutional review board (IRB) [17]. Resources such as Fertile Hope's Cancer and Fertility Referral Guide can help patients and clinicians find centers with IRB-approved oocyte freezing programs [19].

As with embryo banking, oocyte banking may also raise future conflicts for cancer patients. Some of these conflicts are similar to those experienced by patients who have frozen embryos, but others may be unique to patients who elect to freeze oocytes [14]. Patients who freeze embryos can usually have their embryos shipped to any center of their choosing when they are ready to use them. On the other hand, because laboratory protocols for oocyte cryopreservation are not well established, patients may have fewer centers to choose from and may have to return to the center where they had their oocytes initially frozen in order to use them. Also, costs associated with the preparation of frozen oocytes for thaw, fertilization, and transfer may be different than those associated with preparation of frozen embryos [3]. Financial barriers could potentially pose problems for some patients trying to utilize their stored oocytes as fertility treatments are often not covered by insurance [14]. Finally, similar to embryo banking, there does not appear to be any increased risk of congenital anomalies to children born from frozen oocytes, but more follow-up data are needed. Theoretical risks include damage to the meiotic spindle of frozen oocytes that could possibly increase the risk of aneuploidy in embryos resulting

after fertilization [18]. More research is needed to determine the importance of these issues and others in counseling women about their oncofertility options.

Experimental Oncofertility Treatments: Ovarian Tissue Banking

For patients who do not have the time required for embryo banking or oocyte banking, ovarian tissue banking may be an option. This technique involves surgical removal of ovarian tissue which is then cryopreserved and banked for future use. As with oocyte banking, ovarian tissue banking is considered experimental and should only be performed in the context of a clinical trial as research under the guidance of the appropriate Institutional Review Board (IRB) [4, 5]. Unlike oocyte banking, however, much less has been published or proven regarding methods for preparation and use of the tissue or the capability to yield fertilizable oocytes and viable offspring. Although there are a handful of published reports of pregnancies and live births occurring after transplantation of thawed ovarian tissue [20–24], we do not know the denominator that was required to achieve those live births. Finally, while very little is known regarding how patients feel about their stored tissue and what they do with it, it is reasonable to expect that patients may face conflicts and challenges regarding their frozen tissue similar to conflicts women face who elect for oocyte cryopreservation (including the potential for a limited number of centers that can help women utilize the frozen tissue) [14].

Achieving Informed Consent in the Care of Oncofertility Patients

Opinions vary about how truly informed consent is achieved [25, 26]. The Nuremburg Code and the Common Rule both provide guidance for achieving informed consent to participate in research. The Nuremburg Code calls for a research subject to “exercise free power of choice,” have “sufficient. . . comprehension,” and “sufficient knowledge” to make a decision to participate in research [27]. The Common Rule provides additional guidance to many university IRBs in reviewing research consent processes and documents [28]. In accordance with the Common Rule, our own university’s IRB requires consent documents to be written at an appropriate reading level for participants to understand the reasons for, the methods for, the risks associated with, and the safety precautions in place for the research [25, 28]. These guidance documents – supported by a vast professional literature – emphasize the importance of dialogue between the patient and the person obtaining the consent [25, 27]. In the case of oncofertility, this dialogue should include discussion of the points raised in this chapter.

When considering the necessary components for informed consent in the care of oncofertility patients, we recommend beginning with ASRM practice committee guidelines dealing with ART and oocyte and ovarian tissue cryopreservation [3, 5, 7] and the ASRM Ethics Committee statement on fertility preservation and reproduction in cancer patients [8]. ASRM guidelines exist for counseling and consenting patients regarding ART (including procedures requiring oocyte retrieval and fertilization). ASRM has additional practice committee guidelines that define experimental therapies (including oocyte and embryo banking) and identify the necessary elements for discussing oocyte banking with patients. Some of these guidelines address documentation

of disposition decisions for banked embryos, oocytes, and ovarian tissue in the event of a patient's death. These considerations are important for preventing posthumous reproductive decisions that a patient would not have condoned. Documentation of disposition decisions in the event of changing relationships as divorce is also important to protect patients and their partners. Ultimately, standardized consent documents may be helpful in the care of oncofertility patients as these patients may seek future care in a different facility than where they had their gametes or embryos initially preserved.

Experience from the practice of ART may help guide current counseling and consenting of patients in oncofertility. However, further research is needed to determine the best application of ART techniques in oncofertility and to determine the utility of experimental options. Remaining questions that need to be answered include:

- How can oncofertility care be facilitated for women with newly diagnosed cancer?
- When should oncofertility patients be counseled regarding the costs and procedures that may be associated with processing and use of their banked tissues?
- Do strategies for obtaining gametes or tissue affect cancer outcomes?
- How far should the techniques of preimplantation genetic diagnosis be expanded to reduce the risk of cancer in oncofertility offspring?
- What are the best strategies for obtaining gametes and processing them once patients are ready to use them?
- How should banked tissues be handled in oncofertility patients who die before they can use them?
- How important is it to oncofertility patients to have genetically related offspring, and are alternative options like donor oocytes or adoption equally desirable?
- Should strategies for fertility preservation in women with cancer be expanded to all women?

Conclusions

Clinicians caring for oncofertility patients bear the responsibility to ensure these patients clearly understand when their treatment options cross the threshold into experimental techniques. Referring to existing guidelines is helpful for achieving consistency in the counseling and consent of oncofertility patients, however, there are many unknowns in the field of oncofertility that can make it difficult to counsel and consent patients about their options. Legal precedents from more routine cases involving banked gametes and embryos provide examples of specific conflicts about which patients may need to be counseled before they consent to oncofertility procedures, addressing some of these unknowns. Collaborative work and research is necessary to answer remaining questions associated with fertility preservation for cancer patients. Such collaboration will eventually help establish evidence-based guidelines specific to oncofertility patients.

Acknowledgments This research was supported by the Oncofertility Consortium NIH 8UL1DE019587, 5RL1HD058296.

References

1. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006; 24(18):2917–31.
2. Su HI, Sammel MD, Velders L, et al. Association of cyclophosphamide drug-metabolizing enzyme polymorphisms and chemotherapy-related ovarian failure in breast cancer survivors. Fertil Steril. 2009 (In press).
3. Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. Essential elements of informed consent for elective oocyte cryopreservation: a Practice Committee opinion. Fertil Steril. 2008; 90(5 Suppl):S134–5.
4. ACOG Committee Opinion No. 405: ovarian tissue and oocyte cryopreservation. Obstet Gynecol. 2008; 111(5):1255–6.
5. Practice Committee of American Society for Reproductive Medicine; Practice Committee of Society for Assisted Reproductive Technology. Ovarian tissue and oocyte cryopreservation. Fertil Steril. 2008; 90(5 Suppl):S241–6.
6. Thorn P. Recipient counseling for donor insemination. In: Covington S Ed. Infertility counseling. 2nd edn. New York: Cambridge University Press; 2006: 305–18.
7. Practice Committee of the American Society for Reproductive Medicine; Practice Committee of the Society for Assisted Reproductive Technology. Elements to be considered in obtaining informed consent for ART. Fertil Steril. 2006; 86(5 Suppl 1):S272–3.
8. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril. 2005; 83(6):1622–8.
9. https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0. Accessed March 9, 2009.
10. Partridge AH. Fertility preservation: a vital survivorship issue for young women with breast cancer. J Clin Oncol. 2008; 26(16):2612–3.
11. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol. 2008; 26(16):2630–5.
12. Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. Guidelines on number of embryos transferred. Fertil Steril. 2008; 90(5 Suppl):S163–4.
13. Ryan GL, Sparks AE, Sipe CS, Syrop CH, Dokras A, Van Voorhis BJ. A mandatory single blastocyst transfer policy with educational campaign in a United States IVF program reduces multiple gestation rates without sacrificing pregnancy rates. Fertil Steril. 2007; 88(2):354–60.
14. Crockin SL. Legal issues related to parenthood after cancer. J Natl Cancer Inst Monogr. 2005; 34:111–3.
15. Lyerly AD, Steinhauser K, Voils C, et al. Fertility patients' views about frozen embryo disposition: results of a multi-institutional US survey. Fertil Steril. 2008; 2.
16. Ethics Committee and ASRM. Posthumous reproduction. Fertil Steril. 2004; 82(Suppl 1):S260–2.
17. Practice Committee of American Society for Reproductive Medicine. Definition of "experimental". Fertil Steril. 2008; 90(5 Suppl):S181.
18. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online. 2009; 18(6):769–76.
19. Cancer and Fertility Referral Guide. http://www.fertilehope.org/tool-bar/referral-guide.cfm. Accessed September 2, 2009.
20. Andersen CY, Rosendahl M, Byskov AG, et al. Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue. Hum Reprod. 2008; 23(10):2266–72.
21. Bedaiwy MA, El-Nashar SA, El Saman AM, et al. Reproductive outcome after transplantation of ovarian tissue: a systematic review. Hum Reprod. 2008; 23(12):2709–17.
22. Demeestere I, Simon P, Buxant F, et al. Ovarian function and spontaneous pregnancy after combined heterotopic and orthotopic cryopreserved ovarian tissue transplantation in a patient previously treated with bone marrow transplantation: case report. Hum Reprod. 2006; 21(8):2010–4.
23. Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004; 364(9443):1405–10.
24. Meirow D, Levron J, Eldar-Geva T, et al. Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med. 2005; 353(3):318–21.
25. Washington University in St. Louis, HRPO Behavioral Minimal Risk Subcommittee REVIEWER'S GUIDE. hrpohome.wustl.edu/reviewers/Behavminriskreviewerguideline.rtf

26. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA. 2000; 283(20):2701–11.
27. Levine RJ. Consent issues in human research. In: Post SG Ed. Encyclopedia of bioethics. 3rd edn. New York: Macmillan Reference; 2001: 1280–90.
28. US Department of Health and Human Services, Office of Human Research Protections: Title 45 CFR 46. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm. Accessed April 28, 2009.