Chapter 5

Clinical Cases in Oncofertility

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T.K. Woodruff et al. (eds.), *Oncofertility*, Cancer Treatment and Research 156, 55
DOI 10.1007/978-1-4419-6518-9_5.

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

Introduction

As an emerging interdisciplinary field, oncofertility bridges oncology and reproductive endocrinology and infertility with the goal of expanding reproductive options for women with cancer. In this chapter, we present a series of clinical scenarios encountered in medical practice to illustrate some of the complex issues that arise in this field and offer suggestions for patient care. An increased awareness of the difficult issues involved in oncofertility practice should help prepare clinicians for some of the challenges posed by this rapidly expanding discipline. While the four cases presented here are based on true situations, they have been modified to protect the identity of the patients involved.

Clinical Scenario 1

Jennifer is a 24-year-old single female with a history of Hodgkin's lymphoma who was found to have recurrent lymphoma 6 months after chemotherapy (ABVD). Her oncologist recommended bone marrow transplant, a treatment that would almost certainly result in permanent infertility. After a thorough discussion of various fertility preservation options, she decided to bank oocytes. She had a history of regular menstrual cycles and was on day 18 of her cycle. Cetrorelix (Cetrotide!R) 3 mg was administered subcutaneously and she began menstruating 2 days later. Baseline ultrasound revealed an antral follicle count of 3, serum FSH 9.2 mIU/ml, and estradiol 45 pg/ml. Controlled ovarian stimulation was initiated with recombinant FSH at 450 IU per day. Cetrorelix 0.25 mg was started on day 5. On day 10 of stimulation, estradiol was 4,800 and she had 24 growing follicles, the largest measuring 20 mm in mean diameter. Leuprolide acetate was used to trigger final oocyte maturation, she underwent egg retrieval and 15 mature oocytes were vitrified.

Use of GnRH Antagonist for Luteolysis and Cycle Synchronization

In assisted reproduction, gonadotropin-releasing hormone (GnRH) antagonists have traditionally been utilized during ovarian stimulation to prevent a premature LH surge. Recently, the use of GnRH antagonists during the preceding luteal phase has been explored as a technique to improve ovarian stimulation by inducing corpus luteum breakdown and synchronizing the development of the next wave of follicles. While originally intended for poor IVF responders, GnRH antagonists play an important role in the stimulation of cancer patients for embryo and oocyte cryopreservation by shortening

the luteal phase and expediting stimulation and fertility preservation techniques prior to cancer therapy. Taking advantage of its effect on rapid absorption of the corpus luteum, cetrorelix 3 mg is given during the late luteal phase and menses begin a few days later. Patients can then proceed with ovarian stimulation with gonadotropins, and GnRH antagonists are administered when the lead follicle is > 14 mm [1]. The case of Jennifer serves as an example of how luteal GnRH antagonists can be used to shorten the time to stimulation. We have found this protocol to be very useful in cancer patients who have limited time for embryo or oocyte banking prior to life saving cancer therapy.

GnRH Agonist Trigger to Prevent OHSS

Ovarian hyperstimulation syndrome (OHSS) is one of the most serious complications associated with ovulation induction routinely performed as part of fertility preserving techniques such as oocyte and embryo banking. This syndrome may be associated with ovarian enlargement, intravascular depletion, ascites, liver dysfunction, pulmonary edema, electrolyte imbalance, thromboembolic events, and hemoconcentration [2]. While this syndrome is often self-limited with spontaneous resolution within a few days, severe disease may require hospitalization and intensive care [3]. Although the reported prevalence of severe OHSS is low, ranging from 0.5 to 5%, Jennifer's response to stimulation was surprisingly brisk even though her baseline measures of ovarian reserve appeared to be impaired. Selecting the appropriate ovarian stimulation regimen can be challenging in oncofertility because it is important to balance the risk of OHSS and at the same time procure sufficient oocytes or embryos to maximize the chance of a successful pregnancy in the future. The impact of OHSS can be profound in a cancer patient since this syndrome has the potential to delay and complicate planned lifesaving cancer therapy [4, 5].

As an alternative to traditional human chorionic gonadotropin (hCG) administration to simulate the natural midcycle luteinizing hormone (LH) surge, studies have reported that GnRH agonist (GnRHa) administration successfully induces final oocyte maturation and dramatically reduces the risk of OHSS [5–9]. Indeed, it appears that the risk of OHSS is essentially eliminated because GnRHa's induce an endogenous LH surge with a short half-life and reduced luteal phase steroid concentrations [5, 6]. This technique is particularly convenient in cancer patients pursuing oocyte or embryo banking because luteal support is not needed to sustain a pregnancy. While it is helpful to identify patients at high risk of developing hyperstimulation so that appropriate strategies can be implemented, response to gonadotropins and development of OHSS can be unpredictable. Therefore, we have found the use of the GnRHa to trigger the final maturation of the oocytes particularly valuable for many young cancer patients who are at risk for OHSS and the resulting complications. In the case presented, Jennifer was an ideal candidate for trigger with GnRHa because she over-responded to ovarian stimulation. Indeed, despite her high level of estradiol, she did not develop any signs or symptoms of OHSS.

Oocyte Cryopreservation

This case also highlights the important and emerging role of oocyte cryopreservation in oncofertility. Although the first human pregnancy resulting from human cryopreserved oocytes was reported in 1986 [10], oocyte cryopreservation has gained slow support and acceptance as a viable fertility preservation option [11]. Early experience revealed pregnancy rates ranging from 8 to 33% [12–15]. Freezing oocytes rather than embryos offers the cancer patient obvious advantages [16], particularly for those who do not have a partner for sperm source at the time of cancer diagnosis, or who elect not to use donor sperm. Following cancer treatment, frozen–thawed oocytes can be fertilized with sperm from a future partner or donor, enabling the couple to have a child. Freezing oocytes rather than embryos also avoids the ethical and legal issues surrounding embryo storage and disposal, which is a concern for some patients. In Jennifer's case, oocyte banking was the preferred technique for preserving fertility since she was young, unmarried, and did feel comfortable using donor sperm to bank embryos. Unfortunately, the technique of oocyte freezing is more challenging than embryo freezing and therefore success rates have traditionally been lower. Mature oocytes (MII) are highly sensitive to the freeze–thaw process not only because the oocyte has a large water component making it prone to ice crystal formation but also because the meiotic spindle can depolymerize leading to chromosomal abnormalities and the zona pellucid a can harden leading to fertilization failure [16]. Some of these obstacles have been addressed by using techniques such as vitrification and intracytoplasmic sperm injection.

Until recently, the conventional cryopreservation technique has consisted of slow cooling with differing methods of freezing. However, recent studies suggest that oocyte vitrification may hold greater promise for the future. Vitrification uses higher concentrations of cryoprotectants and rapid cooling techniques (–1,500!C/min) that solidify without the formation of ice crystals. Additionally the rapid fall in temperature throughout the transition phase may reduce the thermal stress to the oocyte [11, 17, 18]. To reduce the toxic exposure of cryoprotectants and prevent extreme dehydration, oocytes are in contact with cryoprotectants for a very short period of time [11, 19]. Initial studies comparing outcomes obtained with the slow-freezing method versus vitrification exhibit a trend toward improved survival, fertilization, pregnancy, and implantation rates, suggesting that vitrification may be a more successful technique [20, 21]. We believe that oocyte cryopreservation is an excellent option for adolescents and unmarried young women undergoing fertility-threatening treatments. Continued research is needed to optimize the success of freezing and thawing of human oocytes so that female cancer patients without a partner can maximize their options for future childbearing.

Clinical Scenario 2

Marisol is a 38-year-old woman recently diagnosed with Stage 1 estrogen receptor positive breast cancer who also has a recent history of a deep venous thrombosis requiring anti-coagulation. She has been in a serious relationship with a partner for the past 5 years. In discussion with her willing partner, she elected to proceed with a combination of oocyte and embryo cryopreservation. She underwent controlled ovarian stimulation using a letrozole-gonadotropin protocol and banked 11 embryos and 8

oocytes. She received low molecular weight heparin around the time of her oocyte retrieval and transitioned back to warfarin after stimulation.

Ovarian Stimulation with Aromatase Inhibitors

Invasive breast cancer is the most common neoplasm in women of reproductive age with an estimated 190,000 new cases diagnosed in 2009 [22]. In fact, approximately 25% of women diagnosed with breast cancer in the United States are premenopausal, with 15% under the age of 45 years [23, 24]. In the initial management of breast cancer, surgery is usually followed by adjuvant chemotherapy 4–6 weeks later. Common chemotherapy regimens include an alkylating agent such as cyclophosphamide, which has been found to be highly gonadotoxic. The interval between surgical recovery and chemotherapy often provides sufficient time for ovarian stimulation for embryo or oocyte banking. However, given the potential induction of breast cancer cell proliferation by estrogen [25, 26], there have been theoretical concerns that traditional ovarian stimulation has the potential to cause tumor progression. Therefore, alternative protocols for ovarian stimulation in patients with breast cancer have been under investigation. Aromatase is an enzyme of the microsomal cytochrome P450 superfamily that catalyzes the rate-limiting step in the conversion of androgens to estrogens in many tissues, including granulosa cells of ovarian follicles [24, 27].

Aromatase inhibitors, such as letrozole, markedly suppress plasma estrogen levels by competitively inhibiting the activity of the aromatase enzyme [28] and can be used successfully as ovulation induction agents. In patients with estrogen receptor positive (ER+) breast cancer, the addition of daily letrozole to gonadotropins in ovarian stimulation protocols significantly decreases serum estradiol levels without affecting oocyte or embryo yield [29, 30]. As demonstrated in the clinical case presented, we have found the letrozole-FSH protocol to be useful in women with breast cancer, particularly ER+ breast cancer, who wish to undergo oocyte or embryo cryopreservation. As with traditional stimulation protocols, most patients can complete their cycles without a significant delay in cancer treatment. Although early studies note that ovarian stimulation with letrozole-FSH is unlikely to cause substantially increased risk of cancer recurrence [24, 31], further follow-up studies with larger sample sizes will be needed to determine whether this protocol has an impact on long-term recurrence or survival in breast cancer patients.

Combined Embryo and Oocyte Cryopreservation

Since the birth of the first “test tube baby” Louise Brown, in 1978, the techniques of in vitro fertilization have progressively improved to achieve current pregnancy rates of 40–60% [32, 33]. Thus, the most successful option for fertility preservation in women facing cancer is embryo cryopreservation prior to chemotherapy. In fact, the American Society of Reproductive Medicine considers embryo banking the only “standard” procedure for female fertility preservation and should be offered as a first-line option for appropriate patients [34]. Patients diagnosed with early breast cancer represent a group especially appropriate for embryo cryopreservation because the usual 4- to 6-week delay between

breast surgery and radiation therapy optimally allows for ovarian stimulation, oocyte retrieval, and embryo freezing. While highly successful, embryo banking for female cancer patients is dependent on a male sperm source, obtained either from partner sperm or from a donor sperm bank. In the case presented, Marisol was in a committed relationship but was not yet married. Because she was not entirely confident about her future with her partner, she elected to cryopreserve both embryos and oocytes. The decision to pursue fertility preservation can be overwhelming for many couples, who are suddenly forced into making a "permanent decision" to create biological offspring together. This no doubt heightens the already intense anxiety that such patients experience as they confront their cancer diagnosis and treatment. As the success of oocyte and ovarian tissue cryopreservation continues to improve, we anticipate that women will have more options available to successfully preserve gametes so that they do not have to make such difficult choices. In the meantime, we feel that it is reasonable to offer appropriate patients the option to bank both gametes and embryos since it offers them greater flexibility for future use.

Anticoagulation with IVF Stimulation

Patients undergoing controlled ovarian stimulation with exogenous gonadotropin therapy are at risk of thromboembolic events [35], likely due to a hypercoagulable state induced by supraphysiologic serum estradiol levels and subsequent hemoconcentration [36, 37]. Cancer also increases the risk of thrombosis and therefore this population is more likely to require anticoagulation around the time of fertility preservation techniques compared to the general infertility population. Indeed, we have cared for several cancer patients, like Marisol, who have required therapeutic anticoagulation during ovarian stimulation. While there is limited data on the safety of anticoagulation in the setting of IVF, available published reports are reassuring. For example, Yinon et al. reported no bleeding or thromboembolic complications in 24 women undergoing 73 IVF cycles concurrently treated with gonadotropins and daily low molecular weight heparin (LMWH) at a dosage of 0.6–1 mg/kg/day. The last dose was administered 14–16 hours prior to oocyte retrieval and resumed 12 hours after the procedure [38]. Generally, we have converted patients to twice daily therapeutic low molecular weight heparin 1 week before the anticipated retrieval data and instruct the patient to take her last dose of medication 24 hours prior to the procedure. Low molecular weight heparin is initiated 12 hours following the retrieval and conversion to warfarin may begin. Because cancer patients undergoing embryo or oocyte banking may require anticoagulation during stimulation, it is important for clinicians to be aware of such anticoagulation protocols that have been used successfully in clinical practice.

Clinical Scenario 3

Michelle is an 18-year-old patient with newly diagnosed Ewing's sarcoma requiring high-dose cyclophosphamide and ifosfamide who was referred for fertility preservation given her young age and planned gonadotoxic therapy. According to her oncologist, the patient had a highly aggressive tumor and it was recommended that she undergo immediate cancer treatment. She was extensively counseled about her options including

embryo, oocyte, and ovarian tissue banking. She wished to proceed with ovarian tissue cryopreservation and understood that this was an experimental procedure with the potential for future use if the scientific possibilities advanced.

Ovarian Tissue Cryopreservation

Rather than freezing individual oocytes or embryos, biopsy of the ovarian cortex represents a more efficient way of preserving thousands of primordial follicles at one time. Ovarian biopsies obtained laparoscopically are dissected into small fragments and cryopreserved. As illustrated in Michelle's case, this technique is particularly attractive for girls and single women without a partner and those who cannot delay cancer treatment in order to undergo ovarian stimulation and egg retrieval. In addition, for prepubertal girls, ovarian tissue banking may be the only acceptable method to preserve fertility since ovarian stimulation is not an option [39].

While it might someday be possible to mature oocytes in vitro to achieve pregnancy, autotransplantation of cryopreserved tissue for in vivo oocyte maturation and subsequent IVF appears to be the most promising technique [40]. Ovarian transplantation involves the removal and cryopreservation of ovarian tissue before treatment and the reintroduction of tissue after treatment, either orthotopically or heterotopically, such as in muscle or subcutaneously [41]. Autotransplantation of cryopreserved ovarian tissue also has the potential benefit of restoring temporary endocrine function to cancer survivors who develop premature ovarian failure [42]. In humans, there have been several case reports of ovarian tissue autotransplantation for restoring fertility [43, 44]. In 2004, Donnez et al. reported the first liveborn from orthotopically grafted ovarian tissue fragments to a woman 3 years following chemotherapy and radiotherapy for stage IV Hodgkin's lymphoma [44]. In 2005, another case report was published of a full-term pregnancy following orthotopic autotransplantation of thawed ovarian strips to the cortex of in situ, non-functioning ovaries of a patient with 24 months of ovarian failure following high-dose chemotherapy for Hodgkin's lymphoma [45]. While such reports are exciting, clearly more success must be demonstrated with this technique before ovarian tissue cryopreservation can be considered a realistic option for women faced with cancer.

Similar to oocyte cryopreservation, ovarian tissue cryopreservation is limited by significant technical challenges. First, many oocytes are lost as a result of the freeze–thaw process, but also as a result of initial tissue ischemia at the time of biopsy [46]. Second, the optimal transplantation site has not yet been determined as heterotopic ovarian grafts appear to stimulate differently than expected in traditional IVF. Also, hormone profiles appear different in autotransplanted ovaries as compared to normal ovaries even though neo-vascularization of the ovarian grafts occurs in approximately 1 week and estradiol, FSH, and LH levels revert to premenopausal levels between 3 and 7 months [42, 47]. Perhaps temperature or vascular properties of the heterotopic locations, or the cryopreservation process itself give these grafted ovaries distinct endocrine and oocyte maturation characteristics. Finally, the transplants have short-lived hormonal function, with reports between 9 months and 3 years [48], some even requiring repeat transplantation [49] to maintain function.

Another relevant issue surrounding ovarian autotransplantation is the risk of reseeding cancer to the survivor. Although this phenomenon was not seen when ovarian tissue from lymphoma patients was grafted onto immunodeficient mice [41], the risk is not yet known in humans, and must factor into patient counseling. Currently, the only manner of screening these samples is by conventional microscopic examination of biopsied samples, which is merely an incomplete representation of the entire specimen to be cryopreserved. While many questions remain to be answered with respect to ovarian tissue banking, this option presents a promising experimental technique that is appropriate for some patients.

Clinical Scenario 4

Ann is a 34-year-old woman with a history of recurrent Hodgkin's lymphoma who was interested in learning about her options for fertility preservation. She was in a committed relationship and was scheduled to undergo highdose radiation of the left groin for residual pelvic disease. After reviewing her options, she elected to bank embryos using her partner's sperm. Because her ovarian reserve was impaired from prior chemotherapy with a basal FSH level of 14 mIU/ml, she underwent ovarian stimulation with maximum doses of gonadotropins and was only able to bank three embryos. After embryo banking, she sought additional methods of fertility preservation and elected to proceed with ovarian tissue banking and ovarian transposition. Ten days after egg retrieval, she underwent laparoscopic left ovarian transposition and banked a biopsy of ovarian cortical tissue. She recovered well from the procedures and proceeded with her cancer treatment.

Gonadotoxicity of Cancer Therapy

Ann's case highlights the damaging effect of cancer therapy on the ovaries and the challenges that exist when attempting ovarian stimulation after cancer treatment. The ovary is particularly sensitive to the adverse effects of cancer treatments because of the finite number of germ cells present in the post-natal ovary [50, 51]. Reproductive lifespan is determined by the size of the follicular pool and therefore, cancer treatments that cause follicular depletion are thought to accelerate the onset of menopause [52]. Large retrospective cohort studies assessing menstrual function post-chemotherapy have clearly demonstrated that cancer survivors are at risk of both acute and long-term ovarian failure [53, 54]. The irreversible gonadotoxic effects of some of the chemotherapeutic agents are well documented, particularly for alkylating agents, such as cyclophosphamide, busulfan, and ifosfamide, common components of polychemotherapy for sarcomas, leukemia, lymphomas, and breast cancer [55, 56]. Pelvic radiation therapy is also known to cause follicular destruction followed by reproductive dysfunction [53, 54, 57, 58]. Exposure to 6 Gray of pelvic radiation appears to be toxic to oocytes and many women experience premature ovarian insufficiency [59, 60]. Ovarian failure from these agents appears to be dose-related and the effect is dependent on age at the time of treatment [55, 61]. As seen in Ann's case, even before menstrual dysfunction occurs, cancer survivors have evidence of impaired ovarian reserve compared to similarly aged controls [62–66]. We have observed that the response to ovarian stimulation is often reduced in cancer survivors, yielding fewer oocytes and embryos. Although it is not always possible to predict a

patient's response to ovarian stimulation with accuracy, the patient's age, measures of ovarian reserve, and treatment history (type, cumulative dose, and duration of treatment) are important factors to consider when planning fertility preservation strategies in cancer survivors scheduled to undergo additional gonadotoxic therapies.

Ovarian Transposition

Ann's case also helps to draw attention to ovarian transposition as an important fertility-preserving procedure that is appropriate for selected patients. Oophoropexy and ovarian transposition are surgical procedures that secure the ovary in a fixed anatomic position outside of the radiation field and can be an option for preserving gonadal function in patients undergoing pelvic radiation. Proper surgical technique of transposition is critical to the successful preservation of ovarian function. Pregnancy rates after this procedure was performed in cancer patients less than 40 years of age and have been reported to range from 60 to 89% [67–69, 70]. Ann was a particularly good candidate for this option because she required radiotherapy to the groin. After discussing the proposed radiation treatment with her radiation oncologist, it was clear that her left ovary would be significantly damaged by this treatment. Therefore, to help protect the ovary from radiation exposure, she elected to have a laparoscopic ovarian transposition procedure in which the ovary was moved to the level of the iliac crest.

Selecting More than One Fertility Preservation Option

It is important for the clinician to recognize that fertility preservation techniques are not mutually exclusive, and some patients may be good candidates for pursuing multiple options. For example, in the case presented, Ann not only completed embryo banking, but also banked ovarian tissue and had ovarian transposition surgery. In some cases, patients may elect to pursue multiple options because of poor response to stimulation, or inadequate numbers of oocytes or embryos banked. Others may simply wish to expand their future reproductive options, anticipating continued advancements in reproductive technologies. For example, even a woman who successfully freezes embryos may elect to preserve ovarian tissue in the hopes that the many follicles present in the tissue will provide additional opportunities for having children in the future. Laparoscopic surgery to move an ovary away from the radiation field represents an ideal opportunity to remove and bank ovarian tissue at the same time [69]. It must be recognized that multiple procedures may present additive risk which must be carefully balanced with the potential long-term benefit to the patient. Each clinical situation will present unique opportunities and challenges for fertility preservation and it is important to offer a range of options to patients. Sometimes the best option is not feasible, and alternative, less successful options must be pursued.

Conclusions

Fertility preservation ranks as one of the greatest concerns for women and girls diagnosed with cancer and as technological advancements in the field occur, more patients are pursuing fertility preservation than ever before. Consequently, physicians in the

discipline of oncofertility must be keenly aware of the diverse clinical situations that occur in this field. The clinical scenarios presented in this chapter provide just a glimpse of the complex circumstances confronting the reproductive endocrinologist caring for cancer patients. We have found that a variety of techniques can be used to minimize the risk and maximize fertility preservation options for these patients. It is important to individualize care and be flexible about specific protocols and fertility preservation options. Because of the sensitive and urgent nature of oncofertility, we recommend a team approach to patient counseling. Ideally if time permits, patients meet with physicians, nurses, and mental health professionals in order to discuss fertility preservation options over several visits. This allows for a more comprehensive evaluation to explore and understand the psychosocial and medical needs of each patient. Helping patients navigate fertility preservation options can be incredibly gratifying since it gives patients some control of their reproductive options and provides hope for a “normal life” in the future. We are confident that advancements in the field of oncofertility will continue to expand the reproductive options of all cancer patients.

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

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