Chapter 4
Embryo and Oocyte Banking

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Introduction

Due to significant improvements in cancer treatments, patients affected by oncologic disease are living longer, fuller lives. As a result, the fertility potential of reproductive-age women affected by cancer has become an increasing focus for those who counsel and treat such patients. Advances in reproductive medicine now allow patients diagnosed with cancer during their reproductive years to undergo various fertility preservation techniques, maintaining the potential for childbearing following successful cancer treatment [1–3]. In addition, fertility preservation options, such as oocyte cryopreservation, are now available for those patients with ethical, religious, or social concerns that may prohibit the creation and storage of embryos.

In this chapter, we will focus on the use of embryo and oocyte banking for fertility preservation. The role of ovarian tissue banking and transplantation, as well as the role of medical suppression and ovarian transposition on fertility preservation, will be addressed in other chapters (see Chaps. 5 and 6 in this volume).

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Candidates for Fertility Preservation

Women of reproductive age who are scheduled to undergo medical treatment that could lead to premature decline of ovarian function should be counseled regarding the possibility of oocyte or embryo cryopreservation [2, 4]. Prior to initiating treatment in a patient who desires fertility preservation, a screening examination should be performed in order to confirm that the patient is a good candidate. A baseline fertility assessment, such as an antral follicle count (AFC) and measurement of anti-Müllerian hormone (AMH) and/or day 3 follicle-stimulating hormone (FSH) levels, should be part of the evaluation. In addition, tumor type and stage, timing and gonadotoxicity of chemotherapy, and overall health of the patient should be taken into consideration before initiating fertility treatment. Information collected in this baseline assessment not only aids the physician in selecting appropriate medication doses but also allows for appropriate counseling regarding expected success rates following the procedure.

The standard procedure for embryo and oocyte cryopreservation requires controlled ovarian hyperstimulation and oocyte retrieval, a process that requires approximately 12–14 days. If chemotherapy cannot be postponed for this period of time without potential compromise to the patient's immediate or long-term treatment outcomes, other fertility preservation options should be explored (these options are discussed in greater detail in Chaps. 5, 6 and 7 of this volume).

Patients should be counseled regarding all fertility preservation methods that are applicable to their specific circumstance [5, 6]. Ideally, this counseling should be performed by a physician specializing in reproductive endocrinology and infertility who has experience working with cancer patients. During the counseling session, potential complications of these treatments, such as ovarian hyperstimulation syndrome and intra-abdominal bleeding, should be discussed in detail. Although the incidence of such complications is low, occurring in approximately 5% of cycles, the potential impact of these complications on the patient's current health status and/or plans to move forward with cancer treatment may be significant [7, 8].

Embryo Banking

Since the first reported birth in 1983, several hundred thousand children have been born from cryopreserved embryos created during in vitro fertilization (IVF) cycles. Embryo cryopreservation before chemotherapy is the most well-established and widely available method of fertility preservation [9–11]. This technique involves the collection of oocytes followed by fertilization in the laboratory and subsequent freezing of viable embryos.

Procedure

The embryo banking procedure begins with controlled ovarian hyperstimulation with injectable gonadotropins. The stimulation is usually started the second or third day of full menstrual flow. A classic GnRH antagonist protocol is most often employed as it can be completed quickly and has been associated with lower risk of ovarian hyperstimulation syndrome [12]. A typical cycle is as follows:

- Daily injections with gonadotropins begin on cycle day 2 or 3 and continue daily for an average of 10–12 days.
- GnRH antagonist is added to the medication schedule when the largest ovarian follicle measures 14 mm on transvaginal ultrasound.
- Ovulation is triggered with a single injection of human chorionic gonadotropin (hCG).
- Oocyte retrieval is performed 34–36 h following hCG injection.
- Retrieved oocytes are fertilized in the laboratory. Intracytoplasmic sperm injection (ICSI) may be recommended in order to reduce the risk of fertilization failure regardless of semen analysis results [13].
- Successful fertilization is assessed on the day following oocyte retrieval, and the embryos are monitored in the laboratory until the time of cryopreservation.
- Embryos may be cryopreserved at the 2PN (i.e., prezygote), day 3 (i.e., 8 cell), or day 5 (i.e., blastocyst) stage. The timing of cryopreservation should be individualized and based upon the wishes of the patient and the recommendation of the treating physician.

When beginning stimulation later in the cycle, a modified GnRH antagonist protocol can be utilized, as follows [4]:

- GnRH antagonist is administered as a single 3-mg dose or daily (0.25-mg dose) for 2–3 days to induce menses within 5–7 days, at which time ovarian stimulation can begin [4].
- Alternatively, recombinant FSH and GnRH antagonist can be started at the same time and continued throughout the cycle.
- Ovulation triggering, fertilization, and embryo cryopreservation are carried out in the same fashion as with the traditional GnRH antagonist protocol.

Ovulation induction with leuprolide acetate (single 0.4-mL (2-mg) injection) can be administered in lieu of the traditional hCG ovulation trigger to reduce the risk of ovarian hyperstimulation syndrome in those patients at risk [14].

Cost

The average cost of an embryo cryopreservation (i.e., IVF) cycle ranges from $9,286 to $12,513 [15, 16]. In addition, the initial cost of freezing and storage may add several hundred dollars to the total charge, and there will be additional fees at the

time the embryos are thawed and transferred. Costs vary from center to center, and specifics regarding cost should be addressed with the treating physician. Insurance coverage of fertility-preserving treatments is also widely variable, and questions regarding fertility benefits should be directed toward the patient's insurance provider.

There are some nonprofit organizations dedicated to providing support for patients whose medical treatments present the risk of infertility. These organizations, such as Fertile Hope®, a national LIVE**STRONG** initiative, and the Fertile Action Program, may be able to assist patients with the financial burden associated with undergoing fertility preservation procedures. Information about these organizations may be found online or provided by the treating physician.

Timing

The duration of treatment, from stimulation start to oocyte retrieval, is approximately 14 days. Chemotherapy can be started 1–2 days after oocyte retrieval. In one study, the effect of beginning chemotherapy before complete recovery of the ovaries after stimulation did not show any increase in ovarian damage [17].

Risks

Ovarian stimulation with oocyte retrieval is a relatively low-risk process. However, a small proportion of patients will experience complications such as mild-to-severe ovarian hyperstimulation syndrome or intra-abdominal bleeding. In addition, the procedure may fail to produce retrievable eggs, produce embryos, or result in a pregnancy or live birth.

Success Rates

Published data suggest that women opting for embryo cryopreservation prior to initiation of cancer treatment can expect success rates similar to those of women undergoing IVF for male factor infertility [18, 19]. Parameters to define success, such as oocyte yield, number of embryos cryopreserved, pregnancy rates, and live birth rates, are highly dependent upon the patient's age and baseline fertility evaluation. Table 4.1 shows national success rates for thawed embryo cycles by age.

Table 4.1 Thawed embryo success rates

Age (years)	<35	35–37	38–40	41–42
Live birth/embryo transfer	35.6	30.9	26.1	22.1
Average number transferred	2.0	2.0	2.1	2.3

Data from 2009 SART statistics (21,646 thawed non-donor cycles), *SART* Society for Assisted Reproductive Technology

Oocyte Banking

Recent advances in oocyte cryopreservation have allowed more women to pursue fertility preservation. Because a sperm source is not needed before oocyte cryopreservation, women without a male partner may consider this option. In addition, oocyte cryopreservations present those patients who have ethical or religious objections to the creation of embryos for storage with an alternative treatment choice.

When first introduced in the 1980s, the ability of a cryopreserved oocyte to be fertilized and result in a live birth was compromised by poor oocyte survival and poor fertilization rates [20–24]. However, improvements in cryopreservation techniques have resulted in significantly improved outcomes in patients opting for this method [25–27]. Currently, more than 50% of IVF centers in the USA offer oocyte cryopreservation for cancer patients [28].

It should be noted that the American Society for Reproductive Medicine (ASRM) still considers elective oocyte cryopreservation to be an experimental procedure [29]. The majority of published data describe the outcomes obtained from healthy young oocyte donors, making accurate age-stratified counseling for cancer patients difficult. However, the ASRM does support the use of oocyte cryopreservation as a "fertility preservation strategy for women with cancer and other illnesses requiring treatments that pose a serious threat to their future fertility" [30].

Procedure

The oocyte banking procedure follows the same ovarian stimulation protocols as outlined above for embryo banking. As in the case of embryo cryopreservation, the stimulation start date is usually based on the first day of the last menstrual period.

Following oocyte retrieval, oocytes are prepared for cryopreservation. Two methods of oocyte cryopreservation are currently in use, slow freezing and vitrification [31]. With the slow-freezing method, the oocyte is placed in a low concentration of cryoprotective solution that acts as "antifreeze" by disrupting hydrogen bonds between water, and the oocyte is then slowly frozen in a programmable freezer. In vitrification, the oocyte is placed in a high concentration of cryoprotective agents and then rapidly cooled using liquid nitrogen. The thawing process is also ultrarapid in order to avoid ice nucleation.

Current evidence suggests that vitrification may result in higher survival, fertilization, implantation, and pregnancy rates than slow freezing [32]. Therefore, the vitrification technique is most often utilized for oocyte cryopreservation, although a number of pregnancies have been reported using oocytes that were cryopreserved using the slow-freezing method [31–34].

Cost

The average cost of an oocyte cryopreservation cycle is approximately $7,791 [15]. In addition, the initial cost of freezing and storage may add several hundred dollars to the total charge, and there are additional fees at the time of thawing and transfer. Costs vary from center to center, and specifics should be addressed by the treating physician. As with embryo cryopreservation, insurance coverage is widely variable and questions regarding fertility benefits should be directed toward the patient's insurance provider. Patients may also look into financial assistance programs for cancer survivors as described earlier.

Timing

The duration of treatment, from stimulation start to oocyte retrieval, is approximately 14 days. Chemotherapy can be started 1–2 days after oocyte retrieval. In one study, the effect of beginning chemotherapy before complete recovery of the ovaries after stimulation showed no increase in ovarian damage [17].

Risks

Medical risks are similar to that for embryo cryopreservation. In addition, there is a risk that the oocytes may not survive thawing, not fertilize, or not result in a pregnancy in the future.

Success Rates

To date, over 1,000 live births have been reported as a result of oocyte cryopreservation [35]. Some centers have even reported pregnancy rates similar to those of fresh IVF treatment cycles [36, 37]. These studies were done in young egg donors, and clinical pregnancy rates were reported as high as 83%, however, and there are limited data on women over the age of 35. Success of an oocyte cryopreservation cycle (i.e., oocyte yield) is highly dependent upon the patients' age and baseline fertility evaluation.

Tumor-Specific Considerations

Breast Cancer

Breast cancer is the most common neoplasm diagnosed during the reproductive years, with more than 15% of all new breast cancer diagnoses occurring under the age of 40 years [38–40]. The treatment of invasive breast cancer often includes gonadotoxic agents. As a result, a significant proportion of cancer survivors suffer from premature ovarian insufficiency, making this population an important target for fertility preservation counseling and treatment.

Historically, women with breast cancer have not been offered embryo or oocyte cryopreservation to preserve fertility due to the theoretical risk of tumor progression with the high estradiol levels that often occur during ovarian stimulation. However, standard stimulation protocols can be modified to include the selective estrogen modulator tamoxifen or the aromatase inhibitor letrozole. In one protocol, letrozole (5 mg/day) can be administered at the same time as gonadotropins and continued for 7 days after oocyte retrieval. A recent study showed that the addition of an aromatase inhibitor allowed for ovarian stimulation without significant increases in estradiol levels [41]. As a result, more breast cancer patients are being offered embryo and oocyte cryopreservation.

The timing of ovarian stimulation is of particular importance in patients with invasive breast cancer. In general, the initiation of ovarian stimulation prior to surgical excision is discouraged, especially in those patients with hormone receptor-positive tumors. Instead, ovarian stimulation is best started in the hiatus between surgical excision and chemotherapy. In most cases, surgical excision precedes the initiation of chemotherapy by 6–8 weeks, allowing for sufficient time to undergo ovarian stimulation for fertility preservation. Retrospective studies have shown no significant delay in breast cancer treatment in patients who decide to undergo ovarian stimulation [42, 43]. Furthermore, ovarian stimulation in patients with both hormone receptor-positive and hormone receptor-negative tumors has not been associated with any difference in disease-free survival and overall survival rates compared with those not undergoing fertility preservation procedures [44].

Ovarian Cancer

In the past, the options for fertility preservation in patients with ovarian cancer were severely limited due to the extensive surgical management that treatment of such malignancies involved. The standard of care for ovarian cancer treatment in most cases included total abdominal hysterectomy, bilateral salpingo-oophorectomy, and comprehensive surgical staging. However, less radical surgical management, such as unilateral salpingo-oophorectomy, can be considered in carefully selected cases [45]. Studies examining the 5-year survival rate of patients with early-stage disease showed no difference in survival between those who underwent fertility-sparing

procedures and those who did not [46]. Generally speaking, women with early-stage ovarian cancer may be candidates for fertility preservation via embryo or oocyte cryopreservation.

Hematologic Malignancies

The treatment of hematologic malignancies is frequently associated with significant gonadal toxicity, making fertility preservation counseling and treatment of utmost importance in this population [47, 48]. Complicating the treatment of such patients is the urgency to begin cancer therapy as early as possible after diagnosis. Patients due to undergo immediate cancer treatment are not candidates for embryo or oocyte cryopreservation and should, instead, be offered alternative methods of fertility preservation. For those patients in whom a 2-week treatment delay is acceptable, one can proceed with embryo and/or oocyte cryopreservation using the routine protocol. As patients usually begin chemotherapy shortly after oocyte retrieval, the use of leuprolide acetate for ovulation induction can speed the interval from oocyte retrieval to next menses and minimize the symptoms of ovarian stimulation.

Endometrial Cancer

In reproductive-age women, endometrial cancer tends to be associated with prolonged unopposed estrogen exposure. This may be the result of obesity, anovulation, and/or polycystic ovary syndrome. As these conditions are often associated with infertility, approximately 15% of young patients found to have endometrial cancer are actually identified during the course of infertility workup [49].

Traditionally, the treatment for endometrial cancer has included total hysterectomy and bilateral salpingo-oophorectomy. Alternative treatments that may allow for fertility conservation are available for patients who meet certain criteria. Women with low-grade endometrial cancer may choose to treat their disease with hormonal therapy rather than surgery. In these cases, oral progestational agents may be used in an attempt to convert the endometrium back to a benign state [50–52]. Conservative surgical management with ovarian preservation may also be an option for those patients who are considering the use of a gestational carrier for childbearing.

In those patients who are not felt to be candidates for conservative therapy, ovarian stimulation with embryo and/or oocyte cryopreservation followed by definitive surgical treatment may be employed. A progestin-containing IUD can be placed during the stimulation [53]. It should be noted that there is a significant risk of disease recurrence and/or progression when conservative treatments for endometrial cancer are employed [54]. The decision to proceed with these types of therapy should be done only with the recommendation and guidance of a trained gynecologic oncologist.

Cervical Cancer

Cervical cancer is most commonly diagnosed during the reproductive years and frequently affects women who have not completed childbearing. Conventional treatment for cervical cancer may include radical hysterectomy with or without postoperative pelvic radiation and chemotherapy; however, women with early-stage disease (1A2 and 1B1) may be candidates for more conservative surgical therapy. Radical trachelectomy (surgical removal of the uterine cervix) in carefully selected patients allows for fertility preservation without a significant difference in survival rates compared with those undergoing radical hysterectomy [55, 56].

In patients undergoing hysterectomy, ovarian stimulation can be performed either pre- or postoperatively. When embryo and/or oocyte cryopreservation is pursued postoperatively, the starting point for stimulation must be made serologically, as menses cannot be used as the starting point. In addition, if oophoropexy is performed at the time of hysterectomy, ovarian monitoring and retrieval may need to be done transabdominally. Furthermore, manipulation of the ovaries may affect blood supply and decrease responsiveness to stimulation.

Conclusions

As earlier detection and treatment allow cancer patients to live longer, fuller lives, the need for timely and comprehensive counseling regarding fertility preservation in these women has become an important quality of life issue. Fortunately, the majority of reproductive-age women who are diagnosed with cancer are candidates for fertility preservation, often by embryo and/or oocyte cryopreservation. All women should be made aware of their options for fertility preservation, allowing them the potential to fulfill their reproductive goals.

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