Part II
Fertility Risk and Treatment Options

Chapter 2
Fertility Management for Women with Cancer

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Cancer is now a disease with a variety of treatment options that are leading to longer and more productive lives in survivors. More than 200,000 men and women under the age of 45 years are diagnosed with cancer annually. However, challenges remain for cancer survivors striving to return to normalcy. Infertility can be a consequence of many of the more aggressive chemo- and radiation therapies that prolong and save lives. The ability to easily preserve sperm prior to cancer treatment provides hope at the time of diagnosis to have families later in life for male survivors. A notable example is Tour de France winner Lance Armstrong, who has three children conceived by using sperm collected and frozen days before he underwent the massive chemo- and radiation therapy that saved his life. When faced with a similar devastating diagnosis, women and girls have the same hope for recovery but lack the fertility preservation options that Mr. Armstrong was given. Unlike sperm, the female germ cell, the oocyte or egg, must be retrieved surgically. Moreover, the vast majority of collected oocytes will be immature at collection and cannot be used immediately by a woman who is ready to start a family.

Many of the principles and technologies discussed in this chapter in the context of cancer patients can equally well be applied to women with benign pelvic diseases that threaten their fertility. For example, some women with severe endometriosis or pelvic infection may need to have their ovaries removed as a part of radical surgical treatment for these diseases. In others, during the process of surgically removing ovarian cysts, germ cells can be damaged, thus reducing the woman's fertility. Further, the treatment of benign diseases such as Bechet syndrome and glomerulonephropathies may require chemotherapy that could, just as with cancer patients, reduce ovarian reserve.

Ovarian Physiology

The process of germ cell (oocyte) loss from mid-pregnancy to menopause is a normal physiologic process (Fig. 2.1). At mid-pregnancy, a female fetus has about seven million germ cells that comprise the ovarian reserve. With atresia, this number is reduced to about one million per ovary at birth. The decline in germ cell

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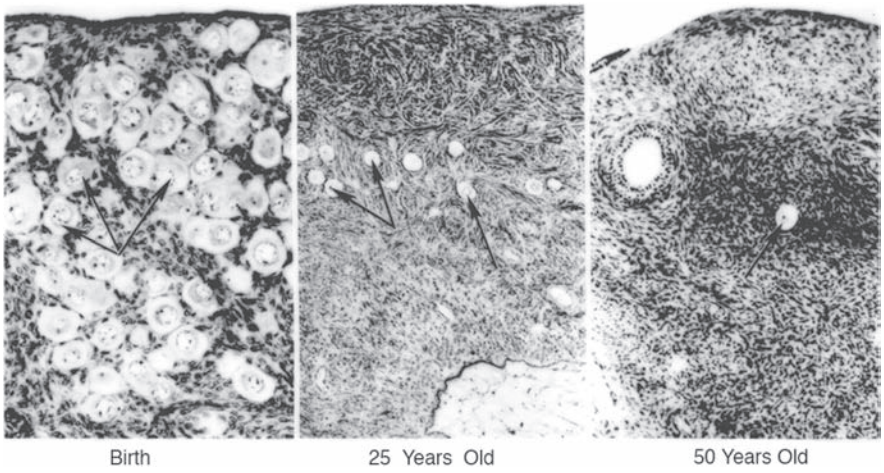

Fig. 2.1 Photomicrographs illustrating the age-related decline of primordial follicle numbers in human ovaries (From Erickson GF. An analysis of follicle development and ovum maturation. Sem Reprod Endocrinol 1986; 4:233–254 by permission of Thieme Medical Publishers, Inc.)

number continues such that by puberty there is a total of about 300,000 germ cells, and by menopause, around 1,000 remain. Thus, prior to spontaneous ovulation, there is a degenerative process of oocyte attrition, the mechanism of which is not well understood. With the onset of menstruation and normal ovulatory function, it is estimated that dozens of oocytes are consumed monthly to achieve a single ovulation. At around age 35–38, there is acceleration in oocyte atresia until the ovarian reserve is exhausted and menopause ensues (Fig. 2.2).

It is evident that, in women, the complete loss of the germ cell population is a result of both spontaneous ovulation as well as an undefined atretic mechanism. While unknown environmental and epigenetic phenomena may be harmful to germ cells, several causative factors such as cancer treatment, including chemotherapy and radiation, as well as elective social activities such as smoking, may accelerate the rate of oocyte loss, thus decreasing fertility and bringing the age of menopause forward.

The decline in germ cell number is mirrored by a decline in female fertility. With increasing age, particularly after the age of 35 years, a woman's natural fertility and chance of success with assisted reproduction declines. Since there can be quite substantial variations in fertility with age, the clinical assessment of a woman's "ovarian reserve" typically involves not just age but also changes in the release of pituitary follicle-stimulating hormone (FSH) and corresponding production of estradiol and inhibin B by granulosa cells within ovarian follicles. As the germ cell pool declines and fewer ovarian follicles are present, there is a decrease in ovarian inhibin B production. Inhibin B provides negative feedback to FSH secretion and hence an increase in FSH can be detected as a result of declining inhibin B. Since FSH values vary during the menstrual cycle, it is standard practice to obtain a measurement of serum FSH on day 3 of the menstrual cycle. An estradiol

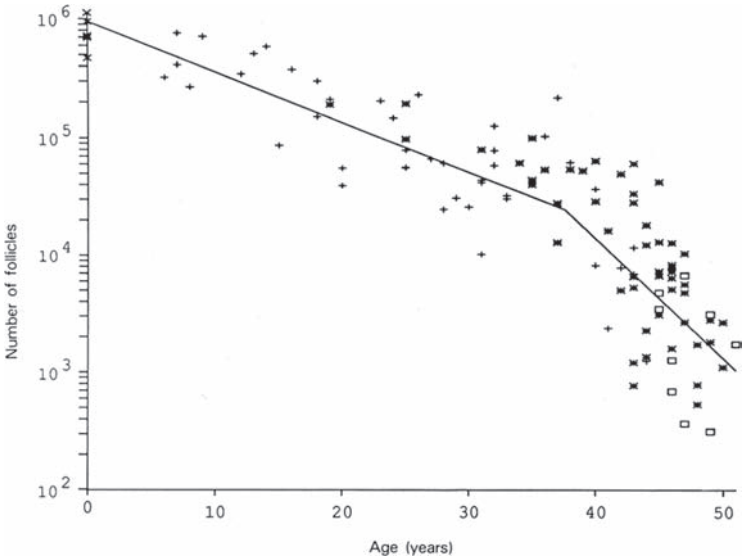

Fig. 2.2 Graph depicting the age-related decrease in primordial follicle numbers with increased rate of loss from around 35–38 years of age (From Faddy MJ, et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 1992; 7(10):1342–1346 by permission of Oxford University Press.)

Table 2.1 Common tools for assessing ovarian reserve in clinical practice

Female age
Day 3 serum FSH (with estradiol)
Transvaginal ultrasound determination of antral follicle count

level is determined on the same day to ensure that the FSH value is accurate and not artificially lowered by a high circulating estradiol level as may occur in the presence of premature follicular development. A more recent addition to the assessment of ovarian reserve has been the ultrasound evaluation of ovarian antral follicle count. For this, transvaginal ultrasonography is performed and the number of small antral follicles in the ovaries is documented. The number declines with age [1,2], and ideally, the observation of a total follicle count of 12 or more from both ovaries is reassuring. Table 2.1 outlines the commonly used strategies for determining ovarian reserve in current clinical practice.

For the patient with a cancer diagnosis, the implementation of treatment in a timely manner is essential in order to have optimal success with life-saving therapies. Therefore, waiting for day 3 in the menstrual cycle to determine FSH and estradiol levels for evaluation of her ovarian reserve is not always feasible. For this reason, when assessing whether or not a cancer patient is a candidate for fertility-preserving therapies, and in order to provide accurate fertility counseling,

the assessment of ovarian reserve by an estimate of age and antral follicle count is of critical importance.

Ovarian reserve testing also has a role following cancer therapy in women medically suitable for pregnancy by helping to determine remaining ovarian function and hence, the appropriate degree of aggressiveness with which one should undertake fertility therapy.

Impact of Cancer Therapies on Ovarian Function

The term "ovarian failure" indicates the irreversible loss of ovarian function with failure of follicular development and ovulation. Concurrently, estrogen production by the ovaries is essentially eliminated and declines to menopausal levels. The loss of ovarian function in a woman less than 40 years of age is considered to be premature ovarian failure. Assessment of the impact of cancer therapies on ovarian function is hampered by inconsistent and varied definitions of amenorrhea and ovarian failure, and in variable time of follow up. Although most studies use a 12-month interval in evaluating post-therapy amenorrhea, it may take up to 16 months to develop in women under 40 years of age [3].

Both chemotherapy and radiation therapies used for the treatment of cancer can lead to premature ovarian failure. The likelihood of this unfortunate consequence depends on the precise therapy and increases with the age of the woman. It should be remembered that because of sporadic ovulation in women with premature ovarian failure, pregnancies have been reported. Even survivors of childhood cancer have an increased risk on premature menopause, which is dependent upon radiation dose to the ovaries, number of alkylating chemotherapy agents used and their cumulative dose, as well as a diagnosis of Hodgkin's lymphoma [4]. Radiation therapy to the pelvis can have a significant direct negative impact on ovarian function. As with chemotherapy, the extent of damage not only depends on the age of the woman but also on radiation dose and field of treatment. Doses as low as 4–6 Gy in adults and 10–20 Gy in children can lead to irreversible decrease in ovarian function with some experiencing ovarian failure [5–9]. The likelihood of ovarian damage can be reduced by surgically moving the ovaries (ovariopexy) away from the radiation field prior to radiation [10]. Total body irradiation of children is particularly likely to lead to ovarian failure, with 90% of those over 10 years of age being affected. It should be remembered that although the impact of irradiation on ovarian function is of profound importance, the uterus can also be damaged by such therapy. Uterine consequences of radiation include decrease in uterine cavity volume [11,12] and decreased blood flow, which may explain the increase in miscarriage and other pregnancy complications seen in women conceiving after pelvic irradiation.

Non-pelvic irradiation can also impact fertility. For example, cerebral irradiation may disrupt central hypothalamic-pituitary regulation of ovarian function resulting in hypogonadotropic hypogonadism [12]. Fortunately, conventional therapies such

as ovulation induction with gonadotropin injections or in vitro fertilization (IVF) and embryo transfer usually suffice to restore fertility.

Breast cancer is the most prevalent cancer to affect women. Although the likelihood of developing this cancer increases with age, about 1 in 3 women are premenopausal at the time of diagnosis [13]. Fortunately, cancer related mortality for breast cancer has decreased dramatically such that with modern management, most women with this diagnosis can expect to live long, productive lives. As a result, premenopausal women with a diagnosis of breast cancer represent a sizeable population concerned about their fertility after cancer therapy [14]. Breast cancer, as well as other cancers, is commonly treated with adjuvant chemotherapeutic agents. Alkylating agents do not have a cell-specific effect and hence have a particularly high propensity for irreversibly damaging resting immature oocytes (primordial follicles). Cyclophosphamide is the chemotherapeutic agent that is most commonly implicated in decreasing ovarian function and does so in a dose-dependent manner.

Age and duration of therapy are other important factors in determining risk of ovarian failure, with older women being more vulnerable than young [15,16]. A clear example regarding the major the impact of age is provided by the study of Goldhirsch et al. [16], in which premenopausal women undergoing classic 6-month cyclophosphamide, methotrexate, and fluorouracil (CMF) adjuvant chemotherapy for breast cancer were studied and found to have a 33% risk of amenorrhea if under 40 years and an 81% risk if older. The same study also demonstrated the impact of duration of therapy, in that those treated for 1 month had less than half the rate of amenorrhea suffered by those receiving 6 months of chemotherapy. The antimetabolites 5-fluorouracil and methotrexate in the CMF regimen have not been shown to cause increased risk of amenorrhea. In combination, these two agents had a 9% amenorrhea rate compared with a 69% rate with CMF in an age-matched population [3].

Preventing chemotherapy-induced ovarian toxicity has been the largely unrealized hope of pretreatment with pharmaceutical agents such as gonadotropin releasing hormone (GnRH) agonists or oral contraceptives. The expectation was that if ovarian metabolism could be made quiescent, then any negative effect of the chemotherapy on ovarian tissue would be minimized. In practice, this theory has not been found to be as successful as once hoped. Only one randomized study has been performed that evaluated 18 women undergoing chemotherapy for Hodgkin's disease [17]. Administration of GnRH agonist prior to and for the duration of chemotherapy was not found to prevent the development of drug-induced amenorrhea during the 3 years of follow up. Incidentally, men were also included in this study, and as with the women, there was no preservation of their fertility with GnRH agonist therapy as documented by the development of oligospermia. In women, this relative lack of efficacy may be explained by the fact that since oral contraceptives and probably GnRH agonists do not preserve ovarian reserve (there is no delay in menopause in users), it is reasonable to infer that they do not prevent the physiologic atrophy of germ cells. Given that chemotherapy damages primordial follicles, it is perhaps understandable why gonadal suppression prior to and during chemotherapy does not prevent ovarian damage.

Current Techniques of Fertility Preservation

Most current methods of preserving fertility in women involve cryopreservation of ovarian tissues. The objective of cryopreservation is to maintain viability of tissue after long-term storage. It is the basis for all forms of fertility preservation for cancer sufferers. Cryopreservation requires cooling tissue from 37°C to the temperature of liquid nitrogen (−196°C), storage at this temperature, and then rewarming to 37°C at some later date. As the temperature of the tissue decreases below the freezing point, the water within the tissue forms ice crystals and expands. This expansion can damage the integrity of membranes and intracellular organelles rendering the cells non-viable. Strategies for the prevention of cell damage associated with freezing include the use of either permeating or non-permeating cryoprotectants. Permeating agents are small molecules that enter the cells and prevent ice crystal formation. Non-permeating agents remain extracellular and draw out the cellular water, hence essentially dehydrating the cells and thus preventing intracellular ice crystal formation.

The conventional method for freezing embryos is called the slow freeze method, and is a technique that can also be used for freezing oocytes and ovarian cortex strips. Cryoprotectants such as dimethyl dulfoxide (DMSO) and, more recently, sucrose are used. The temperature is lowered at a very slow rate of about 0.33°C per minute until reaching −32°C, at which point the sample is put in liquid nitrogen where it is rapidly cooled to −196°C.

Vitrification (rapid freeze) is an alternative strategy for cryopreservation and, as the name suggests, involves the rapid freezing of the sample. High doses of permeating cryoprotectants are used and once allowed to equilibrate, but before toxicity can ensue, the sample is quickly frozen in liquid nitrogen. Rapid thawing is required with this technique to prevent ice crystal formation.

The most successful and only therapeutic option that is widely available for women with cancer wanting to preserve their fertility is to undergo IVF and embryo freezing. This can take precious weeks to accomplish and requires a male partner or the use of donor sperm. The alternatives, which include freezing sections of ovarian cortex or freezing either mature or immature oocytes, still have more limited availability, though with time and increased interest in these techniques both success and availability will increase.

Embryo Freezing

The traditional, and currently the only, well established therapeutic option allowing for fertility after cancer therapy is the storage of frozen embryos. This strategy requires that the patient undergo ovarian stimulation for the in vivo maturation of oocytes and subsequent retrieval of mature oocytes prior to initiation of cancer therapy. The oocytes are fertilized on the day of egg retrieval

and the resultant embryos are cryopreserved. At the time of the patient's choosing, embryos can be thawed and transferred into either the patient's own uterus, providing that her uterus is viable for pregnancy, or that of another woman (gestational surrogate).

The basic technologies necessary for embryo freezing are in clinical use throughout the world on a daily basis. Therefore, availability of services should not be an insurmountable problem. During conventional gonadotropin-stimulated ovulation induction for IVF, it is hoped that a minimum of around 4, and ideally about 10–15, dominant follicles develop. Generally, the actual number of mature follicles attainable decreases with declining ovarian reserve. During the process of ovulation induction, the development of multiple dominant follicles may give rise to substantial increases in ovarian estradiol production due to increased granulosa cell number. In these situations, circulating estradiol concentrations may exceed 3,000 pg/ml. This is substantially greater than that of a natural, unstimulated ovulatory cycle with peak estradiol levels of about 300 pg/ml. This can be a concern for women with estrogen-dependent cancers such as certain breast cancers and benign diseases such as endometriosis. A strategy to successfully induce ovulation for IVF in these women without producing high estradiol levels has been described [18]. It involves adding an aromatase inhibitor to the usual gonadotropin-based ovarian stimulation protocol. Aromatase inhibitors prevent the formation of estrogen from androgen precursors and resultant serum estradiol levels are substantially reduced compared with conventional IVF stimulation and can actually be less than that seen in a natural cycle.

Success rates with frozen embryo cycles depend primarily on the woman's age at the time the eggs were retrieved and fertilized (Table 2.2) and not the age of the woman in whose uterus they are eventually transferred. Once frozen, the embryos can be thawed and transferred years later without a time-dependent decrease in success. For the cancer patient, problems with this strategy are twofold. First, the time required for oocyte maturation with ovulation induction is generally about 2 weeks from the onset of menses. Hence, if the decision to undergo conventional IVF and embryo freezing is made much after about day 3 of the menstrual cycle, the day of the menstrual cycle by when ovulation induction is usually initiated, the patient will have to wait until the onset of the next menstrual period prior to initiating ovulation induction. Second, because embryos rather than oocytes are frozen, there is a need for an acceptable source of sperm. This is not usually a problem if the patient is married or in some other committed relationship. However, for others not in such relationships, the difficult decision of using donor sperm has to be made.

Table 2.2 2005 National frozen cycle results – Society for Assisted Reproductive Technology

	Female age at time of embryo transfer			
Thawed embryos from non-donor oocytes	<35	35–37	38–40	41–42
Number of transfers	8,622	4,379	2,636	898
Percentage of transfers resulting in live births	31.8	27.9	23.1	15.6
Average number of embryos transferred	2.4	2.5	2.6	2.7

Ovarian Tissue Freezing

Ovarian cryopreservation has been shown to be successful in a variety of animal models and to a limited degree in humans. The technique involves the freezing of ovarian cortex segments for later thawing and transplanting either back to the ovarian site (orthotopically) or to some other location (heterotopically). The ovarian cortex is used because it is this part of the ovary that is particularly rich in primordial follicles. In order for cryoprotectants to penetrate the tissue, the cortical strips need to be no more than 2 mm thick. Tissue samples from cancer patients need to be evaluated by a pathologist to detect the presence of any metastatic cancer cells. One of the problems encountered with this technique is a decrease in primordial follicles within the grafted tissue. This is due to hypoxia from a delay in revascularization. The loss of primordial follicles in cryopreserved ovarian cortex strips ranges from 50 to over 90% [19–21], which is reflected in FSH levels that usually remain elevated and inhibin B levels that remain low, even after re-transplantation. Survival of grafts after transplant depends on angiogenesis and neovascularization. As improved understanding of the mechanisms involved spur improved techniques, the outcomes will improve.

Advantages of this technique over the freezing of embryos are that sperm is not necessary at the time of freezing and no delay in cancer therapy is required for oocyte maturation and retrieval. Indeed, ovarian tissue retrieval and freezing can be performed at any time during the cycle, without delaying chemotherapy or radiation therapy. Once the frozen tissue is thawed and transplanted back in to the patient, it is possible that in addition to any fertility benefits, enough estrogen may be produced to at least temporarily treat menopausal symptoms and prevent the onset of osteoporosis. Although the technique is limited by ischemic injury to the transplant tissue, the major theoretical concern with applying this technique to cancer patients is the risk of transplanting back cancer cells with the ovarian tissue.

Pregnancy after orthotopic autotransplantation of cryopreserved human ovarian cortex may be possible naturally. Indeed, this is the ultimate goal of the technique. However, for the purposes of fertility and because of the decrease in germ cell numbers, women undergoing this technique usually require aggressive, high-dose gonadotropin stimulation of the ovarian cortex grafts and are thus usually considered to be in the category of “low responders” with a diminished ovarian reserve. If some ovarian tissue is left in situ at the time of ovarian cortex removal and pregnancy occurs some time after orthotopic ovarian tissue transplantation, it may be difficult to determine whether the source of the fertilized oocyte was the grafted ovarian tissue or the ovarian tissue that was left in situ.

There is much less experience and success with heterotopic autotransplantation. It is possible that the common subcutaneous transplant sites in the forearm or abdomen render the graft likely to fail functionally because of lower temperature and higher physical stress due to inadvertent increases in pressure than normally experienced in the pelvis [22,23]. These grafts need a degree of ovulation induction prior to the retrieval of mature oocytes, which then are used in intracytoplasmic sperm injection (ICSI) and embryo transfer.

Oocyte Freezing

Oocyte cryopreservation is developing as another technology for individuals wishing to preserve fertility but who are not willing to commit to a sperm donor. It can also be an option for those with a partner who, for time constraints, cannot defer cancer therapy for a sufficient time to undergo conventional ovulation induction for IVF and embryo freezing. Because of the complex and fragile nature of the oocyte, oocyte freezing has been technically challenging and success, although improving, has been limited. With this technology, either mature or immature oocytes are obtained and cryopreserved.

Mature oocytes can be obtained by ovulation induction and oocyte retrieval as is done for IVF. However, rather than fertilizing the oocytes prior to freezing embryos, the mature oocytes are frozen. Because of the large size of mature oocytes, they are particularly susceptible to damage during cryopreservation. Ice crystal formation, zona pellucida hardening, and meiotic spindle anomalies have been detected and are associated with reduced oocyte survival and fertilization and increased aneuploidy [24–27]. Although zona pellucida hardening can be overcome with ICSI, there are no good solutions available currently for the disruption of meiotic spindles that occurs when freezing mature oocytes. In addition, although this strategy obviously does not afford any advantage with regard to time needs as compared with conventional IVF and embryo freezing, it does allow a woman to freeze eggs without committing to the source of sperm at that time. Hence, for those not in a committed relationship and wishing to keep their sperm options open, the technology is of potential value.

In order to overcome the time requirements essential for harvesting mature oocytes, a newer strategy for oocyte freezing has evolved. This strategy involves obtaining immature oocytes from unstimulated or minimally stimulated ovaries and after in vitro maturation of the oocytes, freezing either the oocytes themselves or, if sperm is available, embryos. Because of the greater number of small follicles in the ovaries of women with polycystic ovary syndrome (PCOS), most cases described so far have been from PCOS ovaries. After retrieval, the oocytes have typically been made to undergo in vitro maturation (Fig. 2.3) prior to either freezing or fertilization. A less well explored alternative is to freeze immature oocytes soon after retrieval without significant in vitro maturation. After thawing, the oocytes would require in vitro maturation prior to fertilization and embryo transfer. The potential advantage of freezing immature oocytes is that they are smaller and metabolically less active than mature oocytes.

Oocyte freezing strategies have several potential advantages over regular IVF embryo freezing. The time for ovulation induction is not necessary, and for this reason, there is less delay in initiating chemotherapy. Additionally, patients are not exposed to pharmaceutical doses of gonadotropins and high estradiol levels during in vivo oocyte maturation, and commitment to a sperm source is not needed at the time of oocyte retrieval. The relative importance of these advantages varies from patient to patient.

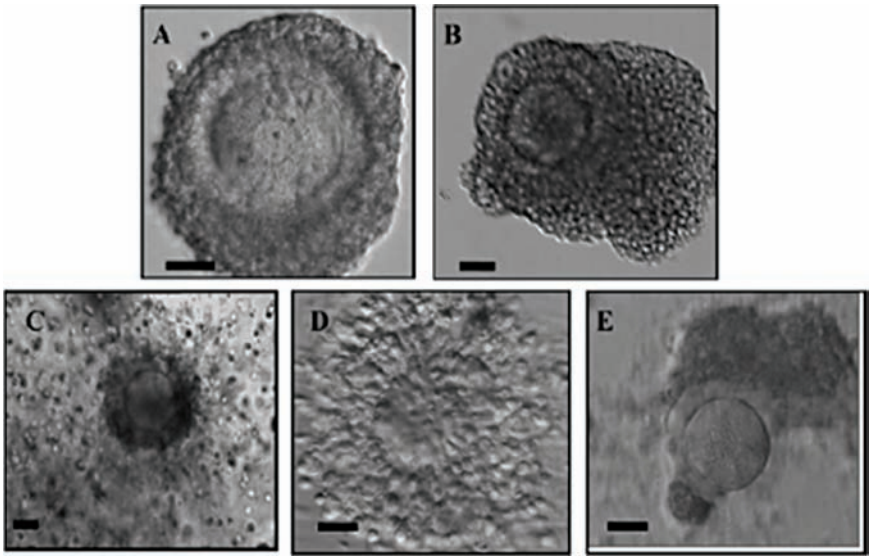

Fig. 2.3 Morphological classification of cumulus-enclosed oocytes retrieved from small antral follicles. Germinal vesicle-stage oocytes are enclosed in 3 (A) to 10 (B) layers of tightly compacted corona cells. (C) Oocytes enclosed in layers of compacted proximal granulosa cells and expanded distal granulosa cells. (D) Oocytes enclosed in expanded cumulus cells (similar to IVF-collected oocytes). (E) Atretic oocytes can be retrieved within fully enclosed cumulus-corona cell layers or partially denuded from cumulus-corona cells (as shown here), or completely naked, with or without a degenerative ooplasmic aspect. All panels, scale bar = 50 μm (From Jurema MW, Nogueira D. In vitro maturation of human oocytes for assisted reproduction. Fertil Steril 2006; 86:1277–91 by permission of Elsevier.)

One study compared chromosome configurations and meiotic spindle microtubules in oocytes that had undergone in vitro maturation to those that had been matured in vivo [28]. The investigators used confocal microscopy and fluorescent immunocytologic staining to analyze oocytes from women with PCOS following retrieval at an immature stage and in vitro maturation. These were then compared with oocytes from women with PCOS that had undergone conventional in vivo maturation with gonadotropin stimulation. The findings were that in vitro matured oocytes were more likely to have abnormal chromosome configurations and disordered meiotic spindle microtubules. Whether the same outcome will hold true for oocytes retrieved from women with a more normal endocrine profile is yet undetermined.

Although success with in vitro oocyte maturation is increasing rapidly, it is still largely limited by the available culture systems. As these and other necessary areas of expertise improve, it is expected that outcomes with this exciting new technology will also improve. Indeed, aspirating immature oocytes and performing in vitro oocyte maturation is already being touted as a useful adjunct to, and a possible replacement for, in vivo oocyte maturation in the current IVF clinic [29–31]. This is especially true for women at particularly high risk for ovarian hyperstimulation

syndrome with gonadotropin-stimulated conventional IVF. With continuing refinement of oocyte freezing technology, the number of oocytes needed for a reasonable chance of pregnancy will decrease. Currently, one can expect a less than 2% chance of pregnancy per thawed oocyte [32]. Despite the current low pregnancy rate per oocyte with the use of aspirated immature oocytes that have undergone in vitro maturation, numerous pregnancies have been reported. There has only been one report of a congenital anomaly following oocyte cryopreservation: a child with an isolated ventricular septal defect [33]. It is also encouraging that, in an albeit limited evaluation, children born as a result of this technology do not appear to show developmental delay during infancy and early childhood [34].

Future Directions

Although the ability to reliably produce successful pregnancies from the harvesting of immature oocytes with subsequent in vitro maturation will likely be the easiest to achieve, there is clearly room for improved success in this and other technologies described in this chapter. Improved outcomes will only come from the deeper understanding of physiologic processes and the development of cryopreservation techniques that are less traumatic to the tissue being frozen. In addition, in the case of ovarian cortex freezing and autotransplantation, improved stimulators of angiogenesis and neovascularization will also be necessary. As these technologies mature, algorithms and guidelines will be developed to ensure that they are used appropriately. Indeed, these strategies may provide a reasonable way for women without cancer or significant fertility-threatening disease to preserve their fertility options for social reasons.

Summary

With time, great strides are being made in the care of cancer sufferers. The longevity and quality of life of these unfortunate individuals continues to improve and the word “cure” is more commonly being heard. In a similar manner, there is also much reason for optimism regarding the future fertility options for patients with cancer as well as for those with other diseases that have a high likelihood of rendering a female infertile prior to completing her family. Figure 2.4 outlines the various cryopreservation technologies currently available. While IVF and embryo freezing remain the gold standard at the present, refinements in in vitro maturation of oocytes and cryopreservation of oocytes and ovarian cortex will lead to improved results and availability of these technologies.

Counseling patients of child-bearing age or their parents regarding future fertility when faced with a life-threatening cancer diagnosis is difficult but extremely important. With modern approaches to cancer care, survival rates have improved

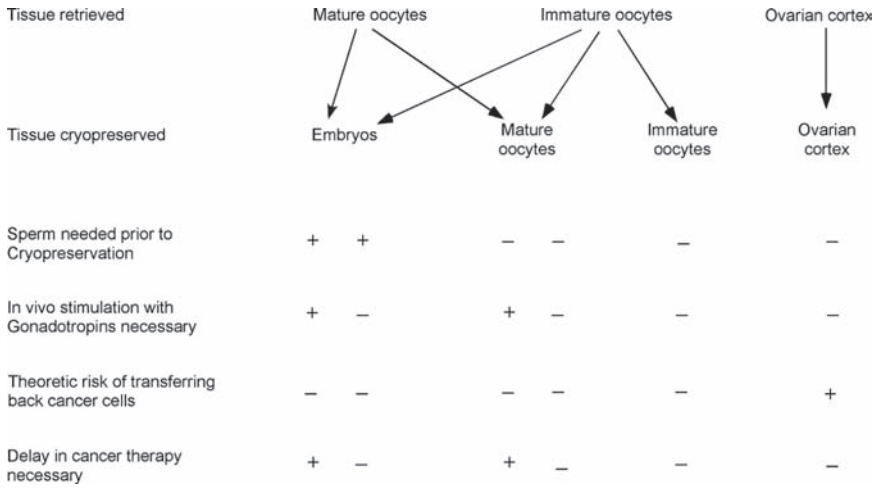

Fig. 2.4 Strategies for the preservation of fertility in women undergoing treatment for cancer or other diseases that are likely to render them infertile

significantly. Therefore, the health care team has a responsibility to provide screening to identify these patients, provide education so that an informed decision can be made as rapidly as possible, and have a team ready to preserve fertility once a decision has been made. With the improvements in fertility outcomes for these patients, appropriate education of key communities, including cancer sufferers and their health care providers, will be necessary to ensure that the issue of fertility after cancer is at least discussed and offered to those in whom it is appropriate.

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