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EDUCATIONAL OBJECTIVES:
After reading the article “Fertility Issues in Cancer Survivorship,” the learner should be able to:
1. Review the gonadotoxic effects of cancer chemotherapy and radiation therapy.
2. Discuss the potential impact of cancer treatment on reproductive health with cancer patients and survivors.
3. Describe techniques to preserve fertility or mitigate the impact of cancer treatment on reproduction.

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Introduction

Breakthroughs in cancer diagnosis and treatment have led to dramatic improvements in survival and the need to focus on survivorship issues. Increasingly, cancer survivorship is encompassing oncofertility, or the management of a person’s reproductive function during and after a cancer diagnosis. This becomes more relevant given that up to 9.2% of patients diagnosed with cancer in the United States are younger than 45 years old. Moreover, up to 1.1% are aged younger than 20 years.1 Given that 5-year survival rates are over 75% for these patients, reproductive issues are increasingly important. Despite technological breakthroughs and the development of new modalities, the majority of cancer treatments still consist of surgery, systemic chemotherapy, radiotherapy, or some combination of these. An acknowledgment and discussion of the changes to a patient’s reproductive health after cancer treatment is essential to providing comprehensive quality care for survivors. The purpose of this review is to aid in pretreatment counseling and, when appropriate, referral for fertility preservation or other strategies that may mitigate the risks to patients’ reproductive, sexual, and overall health. The American Society for Reproductive Medicine (ASRM) and the American Society of Clinical Oncology (ASCO) both advocate for a discussion of fertility preservation options with all patients prior to cancer treatment.2

Female Cancer Survivorship

Although cancer incidence among females of reproductive age has increased by almost 1% annually for the past 15 years and is approaching an all-time high,1-3 cancer mortality among this same population has decreased by 1% to 2% each year over the same period. Annually, over 120,000 women aged younger than 50 years are diagnosed with cancer in the United States.3 Many of the treatments responsible for improved cancer survival rates are gonadotoxic, leading to an increasing prevalence of ovarian damage, with manifestations ranging from subfertility to premature ovarian failure. In addition to the detrimental impact on future fertility, the premature loss of ovarian function can affect bone density, the cardiovascular system, cognition, and overall well-being,4 all of which will profoundly influence the cancer survivor’s quality of life. Moreover, among patients who remain fertile after cancer treatments, subsequent pregnancies may also be at risk of fetal and maternal complications related to certain cancer diagnoses or treatments.
Infertility has been shown to negatively impact quality of life among cancer survivors. The distress resulting from the interruption of fulfilling one’s reproductive goals as a result of a cancer diagnosis and treatment persists several years after the diagnosis, particularly for those who never conceive.5,6 Even a brief discussion of a cancer treatment’s impact on ovarian function and fertility improves patients’ perception of their care, regardless of cancer type, stage, or prognosis.7 This practice has also been a key measure in the Quality Oncology Practice Initiative since 2011.8 Despite its importance, studies have shown that only a subset of oncologists discuss the gonadotoxic effects of cancer treatments with patients of reproductive age, and even fewer refer them for fertility preservation consultations.9,10 While hopefully this practice will improve as new options for fertility preservation transition from experimental to standard of care,11 previous surveys have shown that providers’ discomfort with and avoidance of discussing fertility preservation options stems from a lack of knowledge and familiarity with the options and their success rates.12 Therefore, it is imperative that cancer providers become knowledgeable about not only the adverse effects of cancer treatments on their patients’ reproductive health, but also the various options available and the importance of timely and appropriate referrals to reproductive health specialists.

Impact of Cancer Therapies on Ovarian Function

Human ovarian development is characterized by peak germ cell content during the antenatal period; by birth, 80% of the oocytes have been lost. Despite the presence of 300,000 to 500,000 remaining oocytes at puberty, only 400 to 500 of these oocytes will be selected for ovulation over the next 35 to 40 years, and the rest will be depleted.13,14 As hundreds of follicles are depleted with each menstrual cycle, eventually a threshold is met at which the reproductive potential is diminished and the likelihood of ovulating a good-quality or genetically normal oocyte decreases dramatically. As this trend continues, once only a few follicles remain, a new threshold is reached at which a woman becomes menopausal.15 Ovarian reserve refers to the stores of follicles remaining in the ovaries and can be clinically assessed by a baseline antral follicle count using transvaginal ultrasound, a follicle-stimulating hormone (FSH) level on day 2 to 4 of the menstrual cycle, and/or measurement of anti-Müllerian hormone16 (AMH) on any day of the cycle. The antral follicle count is the number of small (usually 2 mm–10 mm) “selectable follicles” that can be visualized on ultrasound. These follicles are the most sensitive to FSH during the follicular phase,17 and their quantity can be used as a proxy of ovarian reserve.18 A “good” number is usually at least 10 follicles between both ovaries. AMH is produced by the granulosa cells of preantral and antral follicles. Its endogenous role is likely related to autocrine regulation of follicle recruitment, development, and maturation,19 but it has also been found to consistently reflect ovarian reserve with less variation at different times of the menstrual cycle than other measures.20 Gonadotoxic cancer treatments accelerate the cyclical depletion of follicles and their contained oocytes. Should oocyte depletion be accelerated past the menopausal threshold of oocyte depletion, the patient experiences acute ovarian failure; however, should the patient undergo a more moderate acceleration of oocyte depletion without passing the menopausal threshold, the risk is diminished fertility and perhaps early menopause.21

Fertility Risks

For a female cancer survivor to conceive spontaneously, she will require sufficient ovarian follicular reserve, a functioning hypothalamic–pituitary–ovarian axis, a uterus that can accommodate and nurture a developing fetus, and functional organ systems that can adapt to and support the needs of a pregnant body.21 Cancer and related treatments can potentially disrupt any aspect of this delicate balance and limit a patient’s reproductive potential. It is difficult to provide an accurate estimate of the risk of infertility or primary ovarian insufficiency after cancer treatment, since it will vary with the type of treatment and the individual’s baseline age, ovarian reserve, and other reproductive factors.

Baseline ovarian reserve before treatment is one of the most important factors in estimating posttreatment fertility. Older patients typically begin gonadotoxic treatments with less ovarian reserve compared with their younger counterparts, making them more likely to manifest the signs and symptoms of diminished ovarian reserve after accelerated depletion during gonadotoxic therapy.22 Studies have shown the incidence of “acute ovarian failure” among childhood cancer survivors varies from 6.3%23 to 12%,24,25 with ovarian failure or premature menopause defined as the cessation of menses before age 40 years. The cessation of menstrual cycles after gonadotoxic treatment increases to over 50% among patients diagnosed and treated in their 40s.26 It is important to note that these studies describe a much more acute and severe presentation of cancer therapy-induced ovarian failure, defining their target population as those experiencing amenorrhea within 5 years of cancer therapy. These studies likely underestimate cancer treatment’s impact on overall ovarian reserve and fertility, as at the time of their publication, less than 10% of these studies’ population had reached age 40 years. By design, these studies also have overlooked more subtle yet clinically important manifestations of subfertility and diminished ovarian reserve by focusing solely on the resumption of menses.

Resuming menses after treatment is not a direct measure of fertility. Patients should be cautioned that having normal menstrual cycles after treatment is encouraging, but
does not guarantee the ability to become pregnant. In a recent study, classifying ovarian function based on menstrual cycle patterns underestimated the impairment of ovarian function and infertility. At least 40% of women aged 35 years who resumed normal menses following treatment experienced infertility. At least 25% of women treated at age 30 years who resumed menses after treatment experienced clinical signs of early menopause. Animal models have also shown that menses after treatment with chemotherapy and radiation underestimates the depletion of primordial follicles in the ovaries. Thus, using menses as a marker of ovarian reserve very likely underestimates the fertility consequences of cancer treatments.

**Radiotherapy**

Ionizing radiotherapy is an effective cancer treatment because it preferentially damages rapidly dividing cells. Developing follicles, like other non-resting phase cells, are sensitive to radiation, but reserve stores of quiescent primordial follicles are also depleted by ionizing radiation that reaches the gonads, indicating a mechanism of gonadotoxicity that is independent of cell division. In the Childhood Cancer Survivor Study, exposure of the ovaries to radiation proved to be one of the highest risks for acute ovarian failure and premature menopause. Other studies have extrapolated that just 2 to 4 gray (Gy) of ovarian exposure represents the median lethal dose at which one-half of the ovarian reserve is depleted. The severity of depletion depends on the proximity of the ovaries to the irradiated field, the dose of radiation, and the dosing (eg, single high-dose vs several fractionated doses). Older women, presumably due to a lower baseline ovarian reserve, experience ovarian failure with exposure to fewer gray than younger counterparts. A single high dose of radiation is more toxic to the ovaries than multiple fractionated doses of radiation, even of analogous or higher cumulative doses.

Occasionally, shielding of the gonads or adjustment of the radiation field to avoid direct irradiation to the gonads is possible, but in cases with pelvic involvement such as cervical cancer, Hodgkin disease, low spinal cord tumors, or rectal and vaginal tumors, pelvic radiation is unavoidable. In these cases where pelvic radiation is required, oophoropexy has been used since the 1960s to reduce the risk of ovarian radiation exposure by surgically relocating the ovaries from the irradiated field and affixing them to a safer area of the abdomen. This technique is useful for women with adequate baseline ovarian reserve who are anticipating pelvic radiation who are not expected to undergo other systemic, highly gonadotoxic treatments. While oophoropexy does not completely mitigate the risk of ovarian radiation exposure, it does increase the likelihood of preserving ovarian function.

Irradiation of anatomical structures other than the ovaries can also be detrimental to future fertility. Cranial irradiation can cause direct damage to the hypothalamus, pituitary, and the associated vasculature, resulting in a wide spectrum of endocrinopathies that can affect sexual development and fertility. Most directly associated with infertility is hypogonadotropic hypogonadism, but growth hormone deficiency, adrenocorticotropic hormone deficiency, and thyroid-stimulating hormone deficiency can also be observed after cranial irradiation and can negatively affect female reproductive health.

For those women who are able to conceive after prior abdominal or pelvic radiation, there is a higher incidence of miscarriage and infants with lower birth-weight at delivery. These complications are likely multifactorial, but may be associated with the reduced uterine blood flow, uterine volume, and endometrial thickness observed in patients who have received pelvic radiation.

**Chemotherapy**

The gonadotoxic effects of chemotherapeutic agents have been described for at least 50 years, since Louis et al described amenorrhea in conjunction with a hypoplastic endometrium as a side effect of busulfan, an early chemotherapeutic agent used to treat chronic granulocytic leukemia. As with radiotherapy, the gonadotoxicity of chemotherapy is difficult to predict as the detrimental effects on ovarian reserve vary with each patient and are influenced by the dose, type of agents used, number of cycles, underlying cancer diagnosis, and patient’s baseline fertility before treatment. A patient with a robust pretreatment ovarian reserve may maintain her ovarian function and fertility despite a highly gonadotoxic treatment regimen, while a patient with a relatively depleted ovarian reserve may lose ovarian function after receiving a “low-risk” or mildly gonadotoxic treatment.

The mechanism of chemotherapy-induced damage to the ovary varies between different chemotherapy classes, but typically involves either impaired follicular maturation, primordial follicle depletion, or a combination of the two. Either via induced apoptosis or rendering follicles incapable of normal function, chemotherapy accelerates the depletion of functional follicular units, leading to subfertility, diminished ovarian reserve, and potentially even premature menopause. Ovaries in women of reproductive age contain populations of both “recruited follicles,” which are comprised of the developing oocyte and surrounding granulosa cells that rapidly divide in response to gonadotropin stimulation with each menstrual cycle, and quiescent stores of primordial or resting follicles. Both populations are vulnerable to damage or depletion by cancer therapies. By design, many chemotherapeutic agents target cell division.
to preferentially target pathologically rapidly dividing cells (eg, tumor cells). Like other rapidly dividing cells in the body such as the bone marrow, digestive tract, and hair follicles, the dividing cells of recruited follicles are inadvertently damaged by antineoplastic cytotoxic medications.\(^{43}\) Other chemotherapy agents generate non–cell cycle-dependent DNA damage, which is one explanation for the adverse effects on the pool of nonproliferating primordial follicles and the reduced ovarian reserve observed in patients treated before menarche. Alkylating agents, perhaps the subclass of chemotherapeutic agents that is most notorious and most studied for its gonadotoxic effects, induce DNA lesions that cause erroneous cessation of DNA transcription and/or replication manifesting as arrest of the cell cycle.\(^{44}\) Mice studies have shown a dose-dependent depletion of primordial follicles after the administration of cyclophosphamide, even in mice who resumed menstrual cycles, indicating that the depletion of ovarian reserve is not “all or none” and that normal menstruation, and even pregnancy, following chemotherapy does not rule out diminished ovarian reserve.\(^{28}\)

In addition to inducing DNA damage, alkylating agents have also been associated with damage to the ovarian vasculature and fibrosis of the ovarian cortex,\(^{45}\) indicating that there may be additional mechanisms of chemotherapy-induced ovarian dysfunction. Alternative mechanisms of chemotherapy agents’ gonadotoxicity are being elucidated in research, particularly regarding the loss of primordial or resting follicles. One concept, follicular “burn out,” hypothesizes that as developing follicles are damaged by gonadotoxic agents, paracrine signaling from the developing follicle to the stores of resting follicles is disrupted. Loss of this signal may result in abnormally high levels of resting follicle recruitment to become actively developing follicles with each cycle. Subsequently these now actively dividing cells become vulnerable to damage and atresia, diminishing patients’ ovarian reserve during treatment.\(^{56}\)

The mechanism of gonadotoxicity for each subclass of chemotherapy agents is beyond the scope of this review; however, providers should investigate and discuss the relative gonadotoxicity of any protocol with patients of reproductive age. Fertile Hope provides a risk calculator\(^{47}\) that may be a useful resource for patients and providers as a starting point for discussions about the reproductive side effects of various treatment protocols.

**Biologicals**

Biologicals are a relatively new class of anticancer drugs that are typically targeted toward specific receptors, growth factors, or other messaging cascades. Due to their relatively recent introduction into the clinical arena, there is limited literature discussing the potential gonadotoxicity of these agents; however, the existing human and animal reports suggest that the gonadotoxicity is agent-specific rather than a class-wide characteristic. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor, has been described in case reports to induce amenorrhea\(^{48}\) and Genentech, the developer of bevacizumab, recently included a warning describing a higher incidence of acute ovarian failure and a lower incidence of subsequent recovery of ovarian function in patients who received bevacizumab\(^{49}\) in addition to their standard chemotherapy regimen. In contrast, trastuzumab, a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2) in cancers that overexpress the epidermal growth factor, has been shown in limited studies not to increase the risk of acute ovarian failure.\(^{50}\) Imatinib, a tyrosine kinase inhibitor used in patients with leukemia, has conflicting reports of both diminishing\(^{51}\) and even protecting\(^{52}\) ovarian reserve. With the lower toxicity profile of many biological or other targeted therapies, many treatments are continued in the long term as maintenance therapy and this introduces different challenges to fertility. For example, when receiving teratogens such as imatinib\(^{53}\) or tamoxifen, which usually entails at least a 5-year (or potentially longer) course,\(^{54}\) a patient may be torn between discontinuing a maintenance treatment at the risk of recurrence versus forgoing additional time without conceiving, at the risk of ever-diminishing ovarian reserve. With the increasing adoption of biologicals in cancer treatment, novel agent development and approval, and improved testing for ovarian reserve, we look forward to more useful literature regarding the effects of these drugs on fertility, as well as the potential cancer-related risks of withdrawing various maintenance therapies to conceive and carry a pregnancy.

**Fertility Preservation Options**

Infertility may be the most tangible consequence of diminished ovarian reserve following cancer treatment. Patients diagnosed with cancer struggle to identify themselves as normal or healthy, and the potential for future fertility and childbearing helps patients undergoing treatment feel normal again.\(^{55}\) Providers may be hesitant to bring up a topic that may take the focus away from cancer treatment, but many patients want to think about their life after cancer, and a fertility preservation consultation may be a source of hope for these patients. Not surprisingly, in studies surveying cancer survivors, treatment-related infertility was reported to be significantly associated with depressive symptoms and hinders survivors’ quality of life.\(^{56}\) According to the ASCO recommendations for fertility preservation,\(^{2}\) when consenting patients of reproductive age for cancer treatment, oncology providers should discuss the possibility of infertility as well as the options available for fertility preservation. Furthermore, appropriate patients
should be referred to fertility specialists for further counseling and fertility preservation in a timely manner. These same guidelines, updated in 2013,57 identify sperm, oocyte, and embryo cryopreservation as standard practice in contrast with other experimental methods, which is consistent with the recent ASRM opinion regarding oocyte cryopreservation as standard practice.11

It is imperative to the success of fertility preservation that embryos or oocytes are preserved prior to the initiation of gonadotoxic cancer treatment, as a decline in in vitro fertilization (IVF) outcomes following cancer treatment is well documented.58,59 In our experience with patients with breast cancer who require adjuvant chemotherapy, patients undergoing fertility preservation have not experienced any delays in their cancer treatment compared with similar patients not undergoing fertility preservation.60,61 This is attributable to the fact that ovarian hyperstimulation and oocyte retrieval can typically be performed over a 2-week timeframe. Patients anticipating gonadotoxic cancer therapy can usually be fast-tracked to an early consultation and initial evaluation with a provider who practices fertility preservation.

Embryo Cryopreservation

Embryo cryopreservation is the most established fertility preservation technique, having been thoroughly evaluated since the first child was born from a previously frozen embryo in 1984.62 For women who have a partner with whom they wish to reproduce, it may be the optimal method of fertility preservation. Embryo cryopreservation was developed from the effort to use and avoid discarding excess embryos produced from ovarian hyperstimulation as part of IVF cycles. In the United States alone, there are almost 25,000 frozen embryo transfers performed annually, and the rate of live births per frozen embryo transfer is increasingly closer to the live birth rate per fresh embryo transfer.63 In fact, some centers advocate electively using embryo cryopreservation followed by thawed embryo transfers to improve IVF outcomes by optimizing the synchrony between the embryo and endometrium.64

The process leading up to embryo cryopreservation should begin with a consultation with a reproductive endocrinologist experienced with fertility preservation. At this visit, the provider should perform a screening examination and baseline fertility assessment (outlined earlier) as well as take a detailed history pertaining to the cancer diagnosis and treatment plan. This information will help guide fertility specialists in deciding what types of ovarian stimulation are appropriate and the timing of ovarian hyperstimulation, as well as guide any estimation of anticipated success in fertility preservation.65 Patients should be counseled that undergoing fertility preservation by no means guarantees a live birth following cancer treatment. Although it increases the odds of fertility after gonadotoxic cancer therapy, the live birth rate per frozen embryo transfer ranges from 15% to 39%, depending on patient age.59 However, to get to an embryo transfer the patient must have a viable embryo. This requires successful ovarian hyperstimulation, egg retrieval, fertilization, embryo development, embryo cryopreservation, and embryo thaw. Failure can occur at any point in this process. Embryo cryopreservation success varies with the embryo quality as well as each center’s experience and freezing practice, but overall embryo cryopreservation survival rates can surpass 90% in young patients.66

Embryo cryopreservation requires controlled ovarian hyperstimulation and oocyte retrieval, both of which introduce potential risks to the patient. Ovarian hyperstimulation syndrome is a complication of between 1% to 10%67 of IVF cycles. Fortunately, with careful ovarian stimulation and alternative methods of triggering ovulation, most cases consist of mild discomfort; however, the rare severe forms have more serious consequences that may delay planned cancer treatments. While generally very safe, oocyte retrieval introduces the typically low periprocedural risks of bleeding, infection, and damage to nearby structures, as well as the risks of anesthesia. Typically, controlled ovarian hyperstimulation involves daily injections with gonadotropins that are started on cycle day 2 or 3 and continued for 10 to 12 days. In cases in which patients are not in the early follicular phase of their menstrual cycle and there is a limited window of time for fertility preservation before cancer therapy, it is possible to perform controlled ovarian hyperstimulation in the luteal phase after ovulation, as the luteinization of the endometrium is not relevant in cryopreservation cycles.68 There has been debate whether patients with cancer have a poorer response to controlled ovarian hyperstimulation, even before gonadotoxic therapy,69 perhaps due to the effects of an increased catabolic state on the hypothalamic-pituitary axis. While some studies suggest this, other studies have shown no difference in the number of oocytes retrieved from patients with cancer compared with age-matched controls.70,71 In response to the superphysiologic gonadotropins administered, circulating estrogen and progesterone levels are markedly increased relative to physiological levels.72 In hormone-sensitive cancers, notably breast cancer, tamoxifen and letrozole have been used to block the effects of estrogen on breast tissue without adversely affecting the ovarian response.73,74 Patients’ follicle development is monitored with serial transvaginal ultrasounds, and a gonadotropin-releasing hormone (GnRH) antagonist is usually added to prevent early ovulation. When the follicles are at the appropriate size, a single injection of human chorionic gonadotropin or a gonadotropin-releasing agonist is given to trigger oocyte maturation.
Oocyte retrieval is then performed 35 to 36 hours after human chorionic gonadotropin administration before ovulation occurs.75

During the retrieval, follicles are aspirated under transvaginal ultrasound guidance. Following retrieval, oocytes are fertilized either conventionally in a petri dish or with intracytoplasmic sperm injection (ICSI), a procedure in which a single sperm is injected into the oocyte. This method of fertilization is performed if there is concern regarding the sperm quality, although some centers recommend routinely performing ICSI in cases of fertility preservation to maximize the likelihood of successful fertilization.65 Once an embryo is fertilized, it is then cultured until the day of freezing.

When the patient is ready to conceive, her embryos are thawed when her endometrium is at the appropriate stage. The patient’s age, health, reproductive aspirations, and embryo quality are taken into consideration when deciding how many embryos to thaw and transfer into the uterus. During the transfer, a catheter is used to place the embryos into the uterus under transabdominal ultrasound guidance. A pregnancy test is usually performed approximately 2 weeks following the transfer to determine if implantation has occurred.

A male source of sperm is a prerequisite for using embryo cryopreservation rather than oocyte cryopreservation for female cancer patients. While anonymous donor sperm from commercial sperm banks has been used for female patients without a male partner,76 with the recent success of oocyte cryopreservation, this option is being used less frequently.

**Oocyte Cryopreservation**

The ability to consistently freeze oocytes offers female cancer patients the opportunity to preserve their future fertility without the immediate need for sperm, which is a game changer for patients without a sperm source at the time of their cancer diagnosis. Recent breakthroughs in cryopreservation techniques have led to a dramatic improvement in success rates for oocyte cryopreservation. This has led ASRM and ASCO to change the classification of egg freezing from experimental to standard-practice fertility preservation.2,11 While pregnancies resulting from frozen/thawed oocytes were reported just a few years after the first pregnancy from a previously frozen embryo,77 the use of oocyte freezing was not adopted into clinical practice due to inconsistent and generally poor success rates with the initial techniques.78 The oocyte is the largest cell in the body, and its relatively high intracellular water content makes it vulnerable to intracellular ice formation during cryopreservation. Consistent oocyte survival during the freezing/thawing process was initially thought unachievable because of concerns that the formation of ice crystals or the cryoprotectants used to avoid ice formation disrupted the meiotic spindle and predisposed frozen oocytes to aneuploidy.79 However, later studies were more reassuring, showing that there was no evidence of an increase in freezing-associated aneuploidy,80 and ICSI was used to improve fertilization by overcoming the hardening of the zona pellucida often observed after freezing.81 The application of vitrification, a technique that uses rapid cooling to reach freezing temperatures without the formation of ice,82 to oocyte cryopreservation has made the process more successful and consistent. This method has resulted in IVF outcomes using vitrified-warmed oocytes that are analogous to nonfrozen IVF outcomes, with freeze-thaw survival rates of 90% to 95%, and pregnancy-per-transfer rates of 50% to 65% in prospective studies.83–85 Due to higher thaw survival, fertilization, and pregnancy rates, live births following oocyte cryopreservation with vitrification accumulated much quicker than with the older techniques, and current studies have indicated no difference in perinatal outcomes or congenital anomalies among children born from frozen oocytes compared with those born from fresh IVF cycles or spontaneous pregnancies.86

From the patient’s perspective, the oocyte cryobanking process is almost identical to that previously described for embryo cryopreservation except the oocytes are not fertilized prior to freezing. Any patient undergoing oocyte freezing for cryopreservation should be counseled regarding the aforementioned risks of controlled ovarian hyperstimulation and the oocyte retrieval procedure.

Before any oocyte or embryo cryopreservation cycle, patients must be counseled and make decisions regarding the disposition of their gametes and/or embryos in the event of their death or loss of decision-making capacity. Posthumous reproduction, and even the procurement of gametes, is feasible and, according to the ASRM, ethically acceptable if the desired conditions of procurement and use have been explicitly documented by the deceased.87 Patients may also choose to discard or donate cryopreserved gametes or embryos to research, other patients, or other specific uses. Use of cryopreserved embryos created from a patient and her partner’s gametes may also be legally restricted should that relationship end. This potential situation can be avoided by cryopreserving oocytes rather than embryos.

**Ovarian Tissue Cryopreservation and Fertility Preservation in Premenarchal Patients**

Ovarian hyperstimulation has traditionally not been offered to premenarchal patients due to ethical and practical limitations, leaving the over 13,00088 girls who are diagnosed with cancer annually in the United States with experimental options such as ovarian tissue cryopreservation or other less effective methods. While there has been a recent case
report of successful ovarian hyperstimulation and oocyte cryopreservation for a premenarchal patient facing gonadotoxic chemotherapy, this case involved a carefully selected 13-year-old patient who was physically and emotionally mature, already familiar with IVF, and generally deemed well suited to handle the physical and psychological burdens of ovarian hyperstimulation. This case does open the door for further research regarding the application of oocyte cryopreservation in a premenarchal population, and this method can be concurrent with the more common experimental method of fertility preservation in this population, namely ovarian tissue cryopreservation.

Ovarian tissue cryopreservation is an experimental option long considered the only option for fertility preservation for prepubertal girls or women who cannot delay the start of gonadotoxic therapy. By removing either fragments of the ovarian cortex or the entire ovary prior to gonadotoxic treatments, the tissues are spared exposure to these agents and can be cryopreserved until the patient is ready to conceive. After the conclusion of gonadotoxic therapy, the ovarian tissue can be reimplanted and hopefully regain function. In 2000, Oktay et al reported the resumption of ovarian function from a previously cryopreserved autologous transplant of ovarian tissue and in 2004 the first live birth resulting from this technology was reported. Following this live birth, a series of 13 live births resulting from ovarian cortex cryopreservation were reported. In this series, more than one-half of the women who conceived were able to do so without IVF, and ovarian function from the graft was restored for up to 4 years following reimplantation. Other case reports have described restored ovarian function for over 7 years following graft reimplantation, suggesting that these techniques, when more consistent, may also offer relief from the other sequelae of premature menopause. There are well-founded concerns regarding autologous tissue transplantation in patients with a history of cancer. For those patients at higher risk of ovarian involvement (eg, patients with leukemia and lymphoma), improvements in vitro maturation of immature oocytes may someday preclude the need to reimplant ovarian tissue grafts to preserve fertility.

**Preimplantation Genetic Diagnosis**

Both oocyte and embryo cryopreservation require the use of IVF, which enables patients to potentially take advantage of preimplantation genetic diagnosis (PGD), a method of screening embryos or oocytes for genetic abnormalities before transfer into the uterus. PGD was first performed in the 1990s as an alternative to prenatal diagnosis, allowing couples to select embryos before transfer and reducing the risk of having an affected child. When the embryo has developed to a stage with multiple cells, one or several cells can be removed and its DNA analyzed for mutations, including those associated with inherited cancer syndromes. Selected embryos can then be transferred or frozen for future use. While most cancers arise sporadically, 5% to 10% of cancer diagnoses are inherited through currently recognized genetic cancer syndromes. Patients carrying the burden of an inherited cancer, especially those that are autosomal dominant, face difficult decisions regarding family planning. Some choose not to reproduce due to the risk of bringing a child into the world who is more predisposed to suffer from both the psychological burden of an increased risk of cancer and the physical burden of the cancer itself. PGD has been used to screen embryos for several hereditary cancer syndromes (Table 1), and new advances in cancer genetics as well as PGD will likely add to this registry. While some have debated the ethics of screening for genes that only convey an increased risk of cancer, many of which are only manifested in adulthood, others have lauded the ability to offer an individual a chance to spare offspring psychological and physical risk.

**Ovarian Suppression**

Ovarian suppression, either by using a GnRH analog or antagonist, has been used before and during gonadotoxic chemotherapy to mitigate the risk of premature ovarian failure. The efficacy of this strategy during chemotherapy is debatable and studies have shown conclusively that this method does not benefit patients facing radiation-induced gonadotoxicity. Some studies and meta-analyses have shown an increased rate of resumption of menses and ovulation among patients who were cotreated with GnRH analogs during chemotherapy; however, these studies have usually been limited by short follow-up times and no

| GENE | HEREDITARY CANCER SYNDROME |
|------|---------------------------|
| APC  | Adenomatous polyposis of the colon |
| BRCA1 and BRCA2 | Hereditary breast and ovarian cancer |
| CDH1 | Hereditary diffuse gastric cancer |
| MEN1, RET | Multiple endocrine neoplasia |
| PMS1 and PMS2 | Lynch syndrome |
| TP53 | Li-Fraumeni syndrome |
| NF1 and NF2 | Neurofibromatosis |
| RB1 | Inherited retinoblastoma |
| TSC2 | Tuberous sclerosis type 2 |
| VHL | Von Hippel-Lindau disease |

PGD indicates preimplantation genetic diagnosis; CDH, cadherin; TP53, tumor protein 53.
Sexual Dysfunction as an Obstacle to Reproduction

While subfertility may be an overt manifestation of diminished ovarian reserve, it can also be due to sexual dysfunction resulting from the hormonal, physical, and emotional changes resulting from cancer or related therapies. All these consequences can result in a loss of interest in sexual activity or even an aversion to intercourse, potentially causing infertility in the most severe cases.

The temporary hypoestrogenic environment resulting from some cancer treatments can cause vaginal dryness and atrophy, resulting in dyspareunia, vaginismus, a loss of libido, and sexual aversion during and even after the conclusion of treatment. For patients in whom hormone therapy is not contraindicated, a 1-month to 2-month course of systemic or vaginal estrogen therapy (e.g., estradiol at a dose of 2 to 4 mg or a 10-μg tablet of 17β-estradiol inserted vaginally daily initially for 1 to 2 weeks, followed by one-half the dose for a similar time period, followed by a gradual taper) may accelerate relief from these symptoms. Following hormonal therapy, or for those patients who are unable to undergo hormone treatment, non–estrogen-based vaginal moisturizers and lubricants may provide local symptom relief.

With patients who are trying to conceive, it is important to recommend a lubricant (i.e., Pre-Seed or canola oil) that has no adverse effects on sperm.

Nonhormonal consequences of cancer and cancer treatments may also decrease libido and make arousal more difficult. Patients who have undergone surgeries, particularly those affecting the breast, vulva, or vagina, may have an altered perception of their own sexuality and their partner’s sexual interest. Patients who have lost their hair or undergone other physical changes from chemotherapy or radiation or have had their partner assume the caregiver role during cancer treatment may have difficulty perceiving themselves in a sexual role or trusting their partner’s interest in sexual activities. Specific antidepressants with reduced sexual side effects such as bupropion, as well as herbal therapies such as ArginMax and Zestra, have been used to increase libido and sexual enjoyment, but further research of these pharmacotherapies among cancer survivors and those trying to conceive is needed. In addition, ArginMax should be avoided in patients with a history of herpes simplex virus.

Patients who have undergone surgery or radiation to the pelvis may also have anatomical changes such as vaginal shortening, which can make sexual intercourse painful and unpleasant. Providers and patients should refer to online resources available from the International Society for Study of Women’s Sexual Health and the International Society for Sexual Medicine for specific recommendations about psychotherapy and counseling, pharmacotherapy, and alternative positions or techniques, as well as dilator programs for those with anatomical changes. Providers should take an active role in reassuring patients that sexual problems are common and inquiring about sexual function during follow-up visits.

Third-Party Reproduction

Patients who choose not to or are unable to undergo fertility preservation should also be counseled about third-party reproduction options available should they experience infertility after cancer treatment. Third-party reproduction refers to any process in which a third party, or donor, contributes gametes, an embryo, or even a uterus (in the case of gestational carriers), to recipient parents. IVF facilitates using donated sperm or eggs, embryos, or gestational carriers, depending on the unique clinical scenario and need. Alternatively, many patients with cancer who become infertile following cancer therapy also may consider adoption as a way to grow their family; however, a previous cancer diagnosis may unfortunately prevent survivors from using this method to fulfill their family goals. In one survey of adoption agencies, no agency wished to be perceived as cancer-friendly and one-half of the agencies surveyed wished to know the stage of disease and other details regarding any prospective parent’s cancer diagnosis. Furthermore, all agencies surveyed remarked that in many countries from which children are adopted, cancer is perceived as an incurable disease, and a prior diagnosis of cancer may preclude a successful adoption process.

Counseling Before Pregnancy

Prior to undergoing fertility preservation, patients should be counseled about the aspects of a pregnancy that are unique to cancer survivors. Cancer therapies can detrimentally affect major nonreproductive organ systems needed to successfully support the body during pregnancy. For example, anthracyclines and trastuzumab can affect cardiac function, bleomycin and radiation can impact the pulmonary system, and many agents can affect the kidneys. It is important to note potential end-organ toxicities when counseling patients before any cancer treatment, but
obstetricians must also be cognizant of the potential implications of prior treatments on future pregnancies. To date, several longitudinal studies have been performed comparing pregnancies in cancer survivors with those in the general population. The vast majority of pregnancies occurring in cancer survivors are routine and uneventful; however, patients who have undergone abdominal or pelvic radiotherapy have been found to be at a higher risk of preterm birth, low birth-weight offspring, and stillbirth, as well as early neonatal death. Other studies have shown that these risks do not apply to other patients with cancer who have not undergone pelvic radiotherapy, although other studies have shown a possible increased relative risk of preterm delivery or operative vaginal or cesarean delivery, as well as postpartum hemorrhage among cancer survivors. Pregnancies among cancer survivors should typically be managed in consultation with a high-risk perinatology clinic to facilitate frequent surveillance of fetal growth and other fetal monitoring procedures such as regular non-stress testing and amniotic fluid index assessments to ensure uteroplacental adequacy. As the number of cancer survivors of reproductive age increases, the population of pregnant cancer survivors will grow, hopefully leading to more knowledge about obstetrical and neonatal outcomes in this population.

Women’s Fertility After Cancer Treatment
Regardless of the state of ovarian function immediately following gonadotoxic treatment, it is expected that these patients’ stores of primordial follicles have been iatrogenically depleted as a result of their treatment. Consequently, these patients are at risk of accelerated loss of fertility before age 35 years and even premature ovarian failure. As such, patients who have not fulfilled their reproductive goals should be encouraged to do so as soon as possible. Women who are unsuccessful in conceiving or who anticipate a delay before trying to conceive should undergo testing of their ovarian reserves to guide their future family planning decisions.

Male Cancer Survivorship
Cancer survivorship among male patients, especially the aspect of oncofertility, is also becoming increasingly important. Recent estimates suggest that up to two-thirds of all pediatric cancer survivors will face male germ cell dysfunction. Concurrent with an increasing number of male cancer survivors of reproductive age has been the expansion of the age limits defining a male of reproductive age. A consequence of serial monogamy, an increasing prevalence of relationships between older men and younger women, and an increasing frequency of pregnancies at advanced maternal ages, the age of fathers is rising in this country and one can never assume a man’s reproductive goals based on his age. For example, up to 20% of men with an average age of 62.2 years preparing to undergo a radical prostatectomy for prostate cancer reported a willingness to cryopreserve sperm. Similar to guidelines regarding female patients with cancer, both ASRM and ASCO advocate discussing fertility preservation with men prior to the initiation of cancer treatment and both organizations emphasize the safety and reliability of sperm cryopreservation.

Spermatogenesis
During organogenesis in utero, germ cells migrate to the male gonads. Shortly after birth, type A dark and type A pale spermatogonia develop from the gonocytes, the germ cells responsible for gametogenesis. Type A pale spermatogonia divide during every spermatogenic cycle (16 days) beginning at puberty and act as self-renewing progenitors. Type A dark spermatogonia are predominantly mitotically quiescent and serve as a reserve pool that is activated when rapid renewal and proliferation is required, such as at puberty or after injury. As such, they are considered more resistant to the chemical or radiologic insults that may result from cancer treatment.

Cause of Infertility
The etiology of infertility can be due to the underlying malignancy or the treatment. Treatment can take the form of chemotherapy, radiotherapy, surgery, or some combination with different implications based on the exact regimen and modes of administration chosen.

At the time of cancer diagnosis, many men will display abnormal semen parameters. Testicular and hematologic malignancies are the most common cancers that are associated with impaired sperm production. In a review of all patients presenting for sperm cryopreservation in a US sperm bank, over 35% of all men and over 50% of men with testicular cancer had oligospermia (a sperm concentration <20 million/mL). In fact, up to 10% of men may have azoospermia, or absence of sperm in the ejaculate, which has profound implications on fertility preservation prior to cancer treatment. The mechanisms for such impairments are likely multifactorial. Investigators have postulated that factors secreted by tumors (ie, hormones and cytokines) may disrupt spermatogenesis, and that disturbances between the balance of subpopulations of T lymphocytes (eg, Hodgkin disease), hyperthermia, or even central endocrine disruption may all play a role in this process.

Shared etiologies between infertility and tumorigenesis, such as germ cell defects and impaired DNA repair mechanisms, have also been suggested and recent data suggest that men with azoospermia have a higher risk of subsequently developing cancer.
Chemotherapy
The impact of chemotherapy on spermatogenesis is primarily through direct damage to spermatogonia (stem cells). Later-stage germ cells are less sensitive to treatment, and normal sperm counts may be seen after treatment has started. However, such gametes remain susceptible to heritable mutagenic damage, and thus caution should be exercised in using such sperm. The main classes of agents that have been shown to impact fertility include the alkylating agents (eg, cyclophosphamide, ifosfamide, procarbazine, and busulfan) and platinum-based agents (eg, cisplatin). Treatment toxicity generally depends on the regimen and dose. For example, after orchietomy and cisplatin-based chemotherapy for testicular cancer, one group reported normospermia in 64% of patients after 1 year and in 80% of patients 3 to 5 years after treatment. In patients with Hodgkin disease, fertility after treatment is also dependent upon the treatment regimen. Investigators have reported that the older MOPP treatment (mechloretamine, vincristine, prednisone, and procarbazine) caused azoospermia in 100% (47 of 47 cases) of cases 1 year after treatment.136 In contrast, the newer ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) appears to be less toxic to spermatogenesis, as one study showed that 90% of men had no change in their sperm count 1 year after treatment.137

The prognosis after bone marrow transplantation is dependent upon the conditioning treatment. Cyclophosphamide alone resulted in 90% of men achieving a recovery of sperm production. However, men receiving cyclophosphamide with busulfan or thiotepa had a 50% chance of recovery of sperm in the ejaculate but with abnormal semen parameters. Cyclophosphamide with total body or thoracoabdominal irradiation had only a 17% overall recovery rate with no sperm in the ejaculate recovered within 4 years of treatment.138

Radiotherapy
Spermatogonia are sensitive to radiotherapy, whether it results from direct exposure or scatter when other organs are targeted. Here again, the cumulative dose is important. In contrast to other organ systems where fractionation of radiation reduces damage, radiation doses to the germinal epithelium of the testes given in fractionated courses can increase gonadal damage compared with single doses. A dose of just 0.15 Gy can lead to a reduction in sperm count while a dose of 0.35 Gy can cause reversible azoospermia. Doses up to 2.5 Gy can lead to prolonged and likely permanent azoospermia while a dose of greater than 20 Gy is generally considered to be a lethal dose for spermatogonia.139,140

Both direct and indirect testicular exposure is important. For example, men undergoing external-beam radiotherapy to the prostate (70 Gy) display impaired spermatogenesis likely due to scatter to the gonads.141 In contrast, 4 patients receiving more localized brachytherapy showed no change in semen parameters at 6 months.142 The testicular toxicity resulting from the scatter of radiotherapy for rectal cancer was measured indirectly by examining the cumulative dose the testes received during the course of 50-Gy pelvic external-beam radiotherapy. The testicular dose ranged from 0.7 to 8.4 Gy, with 73% of patients receiving more than 2 Gy (a level generally considered to carry a significant risk for permanent azoospermia).143

Similar to the aforementioned effects seen in women undergoing brain radiotherapy, brain irradiation in males can impair pituitary function and lead to secondary hypogonadism.144 While replacement of gonadotropins is often successful, semen cryopreservation prior to therapy remains a superior option. Testosterone replacement is not recommended for those who desire fertility as it can impair spermatogenesis.145

Methods of Gonadal Protection
When possible, gonadal shielding remains the standard of care during radiotherapy. Given the sensitivity of the testes to even low levels of radiation scatter, lead shielding of the gonads can significantly improve a man’s fertility prognosis. Hormone suppression prior to chemotherapy has also been explored given that quiescent cells are more resistant to toxic agents compared with rapidly dividing cells. Thus, by suppressing the hypothalamic-pituitary-gonadal axis, the spermatogonia may enter a less susceptible state. However, human trials have not demonstrated a clear benefit to hormonal suppression with agents including GnRH agonists, androgens, and antiandrogens.146-148

Surgery
Surgical cancer treatment can impair sperm delivery and production. Radical pelvic surgery as performed for prostate, bladder, or rectal cancer can impair erections. In the case of prostate and bladder surgery, with the prostate and seminal vesicles removed, the continuity of the genital tract is disrupted. As such, ejaculation is lost and with it seminal emission. While sperm cannot be expelled from the body, spermatogenesis normally persists. As such, adjuvant sperm extraction procedures will be required for conception. For example, testicular sperm extraction (TESE) involves an open incision into the scrotum and testis to remove numerous seminiferous tubules with their included sperm. Testicular sperm aspiration is another option whereby a small needle (16-gauge to 23-gauge) can be passed into the testicle to retrieve sperm-bearing seminiferous tubules. Still another method involves extracting sperm directly from the epididymis, the primary site of sperm maturation and motility acquisition. The epididymis
can be accessed via a small-caliber needle (23-gauge to 25-gauge) in a technique known as percutaneous epididymal sperm aspiration. Alternatively, microscopic epididymal sperm aspiration involves the use of an operating microscope to extract sperm from individual epididymal tubules generally in greater numbers than can be achieved percutaneously. While the sperm extraction method is generally left to the one that maximizes physician and patient comfort, the use of the microscope-assisted approach limits the amount of tissue required, which may reduce scarring and allow for multiple retrievals more easily.

Retroperitoneal lymph node dissection can interrupt sympathetic nerves that control normal ejaculatory processes, leading to anejaculation or retrograde ejaculation. Importantly, advances in surgical techniques and the understanding of anatomy have reduced the incidence of retrograde ejaculation to less than 5% in some studies. Medical therapy in the form of sympathomimetics may improve ejaculatory efficiency and allow for the antegrade transit of sperm in some patients with ejaculatory dysfunction following retroperitoneal lymph node dissection. If unsuccessful, electroejaculation (EEJ) can be used to achieve antegrade ejaculation. EEJ involves directly stimulating the nerves involved in emission and ejaculation transrectally with progressively higher electrical currents until success is achieved. As might be expected, neurologically intact men require general anesthesia for the procedure. Unilateral orchiectomy for testicular cancer or tumor infiltration can impair sperm production while bilateral orchiectomy will eliminate it. Prior to orchiectomy, semen cryopreservation remains the best option. If no sperm is produced in the ejaculate, a TESE to identify pockets of intact spermatogenesis within the testis has been employed successfully.

Gonadal Endocrine Function

In addition to sperm production, it is also important to consider gonadal endocrine function after cancer treatment. Chemotherapy and radiotherapy administered for testicular cancer can directly damage testicular Leydig cells and impair testosterone production. After radiotherapy for rectal cancer, one study suggested that testosterone levels declined by 78%. Both radiation and chemotherapy regimens have been implicated in the increased rates of low testosterone levels noted in men treated for lymphoma. Hypogonadism can impair libido and sexual function, including erectile dysfunction and ejaculatory disorders. In addition, low testosterone levels have been associated with higher rates of cardiovascular and overall mortality. It is also important to note that low testosterone levels have been implicated as the mechanism for the higher rates of the metabolic syndrome noted in long-term survivors of testicular cancer.

Close surveillance and treatment of testicular failure after cancer treatment remain important considerations both for quality of life as well as overall health. While testosterone replacement therapy remains a viable option, the contraceptive properties of testosterone warrant careful attention and a discussion of options, especially in men of reproductive age.

In fact, trials have explored intramuscular testosterone therapy as a means of male contraception. Most studies have demonstrated that over 90% of men will become azoospermic on such a regimen, with the remaining individuals having severely impaired sperm counts. In such cases in which low testosterone levels require treatment, referral to reproductive specialists or endocrinologists should be made.

Methods of Collection

The gold standard for fertility preservation is cryopreservation of ejaculated sperm. For men who are unable to ejaculate, assisted ejaculatory techniques can be employed such as EEJ (previously discussed) or penile vibratory stimulation (PVS). PVS involves the use of 1 or 2 vibrators applied directly to the phallus. Activating normal spinal reflex arcs can allow normal ejaculation. Such methods can be used for patients unable to masturbate or those with neurologic lesions. Alternatively, percutaneous or open testicular or epididymal sperm extraction techniques can be used. For azoospermic men, TESE (or OncoTESE when azoospermia is related to cancer diagnosis) can identify sperm in about 40% of men and harvested sperm can then be frozen for use at a later date.

After cancer treatment, sperm extraction techniques are still possible. While sperm production may be impaired after treatment such that too few sperm are produced to reach the ejaculate, TESE can be used to identify pockets of sperm production within the testis that can then be used for IVF with ICSI. Importantly, clinical parameters such as laboratory values (eg, FSH, luteinizing hormone, or testosterone) or testis volume have not been shown to provide valuable prognostic information regarding surgical sperm yields. Series have suggested that 37% to 65% of men who are azoospermic after cancer treatment will have sperm identified by TESE. The use of an operating microscope is thought to improve sperm yields by allowing the urologist to identify the seminiferous tubules most likely to contain sperm. It is important to note that most data regarding recovery of fertility and sperm counts after chemotherapy and radiotherapy (as listed above) rely...
on ejaculated sperm counts and not the result of testicular sperm extraction to assess a man’s fertility potential. It is likely that the use of more advanced and invasive techniques to identify more limited quantities of sperm production can allow a great percentage of men the opportunity for biologic paternity.

Use of Cryopreserved Sperm
Depending upon the quantity and quality available for cryopreservation, sperm is often preserved in several aliquots. In men with adequate counts (generally greater than 5 million motile sperm), the sperm may be used for intrauterine insemination, a technique in which the semen sample is concentrated and then inserted with a small catheter through the cervix in an office-based procedure. The sperm are placed directly into the woman’s uterus at midcycle, with or without medically assisted ovulation. In those with lower counts, IVF or ICSI remain excellent options for paternity. ICSI, a technique that has revolutionized treatment for male factor infertility, involves the injection of a single sperm into an egg to fertilize it, bypassing the need for normal semen parameters. It is important to know that in all cases of surgically extracted sperm (ie, TESE or other methods of sperm aspiration), IVF with ICSI is required. Proper counseling of men interested in such treatments is crucial given the costs associated with advanced reproductive techniques. In addition, data supports that treatment outcomes are excellent regardless of the extraction technique used.

The subsequent use of cryopreserved sperm is important to investigate and is reported to be low in most series. In a study from the United States involving 164 men who stored sperm between 1993 and 2003, only 6 (3.7%) used their sperm during the follow-up period. Most other series from centers around the world report similar results, with 3.6% to 16% of patients reportedly using their sperm. While the follow-up has been criticized as being short, the results are sobering. Whether men recover spermatogenesis, change reproductive goals, or develop continued health ailments that prevent parenthood is uncertain.

Health of the Offspring
The potential damage to sperm DNA integrity from cancer treatment has led to concerns about the health of the offspring of cancer survivors. To date, most studies have been encouraging. A case-control study comparing 2198 offspring of cancer survivors with 4544 offspring of controls in the United States found no difference in disease risk between the 2 groups. Similarly, a retrospective cohort study of 470 cancer survivors and 4150 population-based controls also found no difference in congenital malformations or prematurity. In contrast, the largest study on the topic published to date found a small increased risk of birth abnormalities in the offspring of men with a history of cancer. The authors investigated all singleton births from 1994 to 2004 in Sweden and Denmark (n = 1,777,765). They found that those children sired by fathers with a history of cancer (n = 8670) had a 17% increased risk of congenital malformation (relative risk, 1.17; 95% confidence interval, 1.05-1.31). While statistically significant, the change in the absolute risk (3.7% vs 3.2%) remained modest. Thus, the ASRM currently states that “Concerns about the welfare of resulting offspring should not be cause for denying cancer patients assistance in reproducing.”

Fertility Preservation in the Prepubertal Male
The current methods for fertility preservation are only available for men who have undergone puberty and thus initiated spermatogenesis. The age of spermarche (age of onset of sperm production) is generally considered to be between 12 to 14 years but can be variable. It can often be difficult to assess when this process has started and to whom assisted ejaculation (ie, EEJ or PVS) or sperm extraction procedures should be offered. Physical examination findings in boys, such as a testes volume of at least 10 cm³ or Tanner stage II development or greater, can be useful factors to guide clinical decisions.

At the present time, cryopreserved testicular tissue from prepubertal boys cannot be used in a clinical setting. Current uses of such tissue are considered experimental. Ethical issues involved in its procurement, including obtaining informed consent, are complicated and generally must be collected under an Institutional Review Board-approved protocol.

Several strategies have been proposed for the use of harvested spermatogonial stem cells from prepubertal boys to produce mature sperm:
1. Transplant back into testis after gonadotoxic therapy.
2. Generate spermatozoa from spermatogonial stem cells in vitro.
3. Graft immature tissue into another organism when fertility is desired.
4. Organ cultures and 3-dimensional matrices.

Investigators have succeeded in transplanting spermatogonial cells back into stem cell-depleted testes of nonhuman primates. While promising, the risk of reintroducing hematologic malignancy remains. In the mouse model, neonatal murine testicular tissue used to generate functional sperm cells in vitro was used to produce healthy, fertile offspring. While the field is rapidly advancing, at the current time there is no clinical application for immature testicular tissue. Details relating to the amount of tissue and optimal cryopreservation parameters are currently under investigation.
Conclusions

With improved cancer treatments, attention has recently turned to issues related to survivorship. Given the importance that fertility has on quality of life and the current techniques available for gamete procurement and cryopreservation, all patients of reproductive age should be counseled about fertility preservation options as well as the systemic consequences of gonadotoxic cancer therapies prior to initiating treatment.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62:10-29.
2. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24:2917-2931.
3. National Cancer Institute. Surveillance, Epidemiology, and End Results. SEER 9, Fast Stats. seer.cancer.gov/lateststats/selections.php?. Accessed June 20, 2013.
4. De Vos M, Devroe P, Fauser BC, Primary ovarian insufficiency. Lancet. 2010;376:911-921.
5. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer: A pilot survey of survivors’ attitudes and experience. Cancer. 1999;86:697-709.
6. Canada AL, Schover LR. The psychosocial impact of interrupted childbearing in long-term female cancer survivors. Psychon­cology. 2012;21:134-143.
7. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues and experiences. Cancer. 2004;10-29.
8. The Quality Oncology Practice Initiative. Summary of the Measures. qopi.asco.org/Summary_000.pdf. Accessed June 20, 2013.
9. Quinn GP, Vadaparampil ST, Gwede CK, et al. Discussion of fertility preservation with newly diagnosed patients: oncologists’ views. J Cancer Surviv. 2007;1:146-155.
10. Duffy CM, Allen SM, Clark MA. Discussion regarding reproductive health for young women with breast cancer. J Clin Oncol. 2004;22:4174-4183.
11. The Quality Oncology Practice Initiative. Summary of the Measures. qopi.asco.org/Documents/QOPISpring2011Measures-Summary_000.pdf. Accessed June 20, 2013.
12. Quinn GP, Vadaparampil ST, Gwede CK, et al. Discussion of fertility preservation with newly diagnosed patients: oncologists’ views. J Cancer Surviv. 2007;1:146-155.
13. Quinn GP, Vadaparampil ST, Gwede CK, et al. Discussion of fertility preservation with newly diagnosed patients: oncologists’ views. J Cancer Surviv. 2007;1:146-155.
14. Quinn GP, Vadaparampil ST, Gwede CK, et al. Discussion of fertility preservation with newly diagnosed patients: oncologists’ views. J Cancer Surviv. 2007;1:146-155.
15. te Velde ER, Scheffer GJ, Dorland M, Broekmans FJ, Fauser BC. Developmental and endocrine aspects of normal ovarian aging. Mol Cell Endocrinol. 1998;145:67-73.
16. La Marca A, Sighinolfi G, Radi D, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update. 2010;16:113-130.
17. Gougeon A. Regulation of ovarian follicular development in primates: facts and hypotheses. Endocr Rev. 1996;17:121-135.
18. Broekmans FJ, Faddy MJ, Scheffer G, te Velde ER. Antral follicle counts are related to age at natural fertility loss and age at menopause. Menopause. 2004;11:607-614.
19. Seifer DB, MacLaughlan DT. Mullerian inhibiting substance is an ovarian growth factor of emerging clinical significance. Fertil Steril. 2007;88:539-547.
20. Seifer DB, Baker VL, Leader B. Age-specific serum anti-Mullerian hormone values for 17,120 women presenting to fertility centers within the United States. Fertil Steril. 2011;95:747-750.
21. Levine J. Gonadotoxicity of cancer thera­pies in pediatric and reproductive-aged females. In: Gracia C, Woodruff TK, eds. Oncofertility and Medical Practice: Clinical Issues and Implementation. New York: Springer; 2012:3-12.
22. Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA. 1988;259:2123-2125.
23. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metab. 2007;92:1712-1728.
24. Sklar CA. Maintenance of ovarian function and risk of premature menopause related to cancer treatment. J Natl Cancer Inst Monogr. 2005;34:25-27.
25. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst. 2006;98:890-896.
26. Goodwin PJ, Ennis M, Pritchard KL, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol. 1999;17:2365-2370.
27. Letourneau JM, Ebbel EE, Katz PP, et al. Acute ovarian failure undergraduates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. Cancer. 2012;118:1933-1939.
28. Meirion D, Lewis H, Nugent D, Epstein M. Subclinical depletion of primordial follicular reserve in mice treated with cyclophosphamide: Clinical importance and proposed accurate investigative tool. Hum Reprod. 1999;14:1903-1907.
29. Boguski RG, Wade JC, Fraser HM, Sandow J, Faddy MJ. Impact of congenital or experimental hypogonadotropism on the radiation sensitivity of the mouse ovary. Hum Reprod. 1997;12:2483-2488.
30. Meirion D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update. 2001;7:535-543.
31. Green DM, Sklar CA, Boice JD, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27:2374-2381.
32. Wallace WH, Sklavos SM, Hendry JH, Morris-Jones PH, Gattamani HR. Ovarian failure following abdominal irradiation in childhood: The relationship of the human oocyte. Br J Radiol. 1989;62:995-998.
33. Wallace WH, Sklavos SM, Hendry JH, Morris-Jones PH, Gattamani HR. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005;62:738-744.
34. Thibaud E, Rodriguez-Macias K, Trivin C, Esperou H, Michon J, Brauner R. Ovarian function after bone marrow transplantation during childhood. Bone Marrow Transplant. 1998;21:287-290.
35. Garer W, Gab Z, Garer H. Needle oophoropexy: A new simple technique for ovarian transposition prior to pelvic irradiation. Surg Endosc. 2011;25:2241-2246.
36. Harad H, Loven D, Herskovitz P, Bairey O, Yagoda A, Levavi H. An evaluation of lateral and medial transposition of the ovaries outside of radiation fields. Cancer. 1994;74:774-779.
37. Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. Am J Obstet Gynecol. 2003;188:367-370.
38. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer. 2010;17:141-159.
39. Hawkins MM, Smith RA. Pregnancy outcomes in childhood cancer survivors: probable effects of abdominal irradiation. Int J Cancer. 1989;43:399-402.
40. Bath LE, Critchley HO, Chambers SE, Anderson RA, Kelmar CJ, Wallace WB. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. Br J Obstet Gynaecol. 1999;106:1265-1272.
41. Louis J, Limarzi J, Best WR. Treatment of chronic granulocytic leukaemia with Myleran. Arch Intern Med. 1956;97:299-308.
42. Olive DL. Reproductive physiology. In: Berek JS, ed. Berek and Novak’s Gynecology and Infertility. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 1999;114-120.
apy for Hodgkin’s disease. Hum Reprod. 1993;8:2080-2087.
44. Epstein RJ. Drug-induced DNA damage and tumor chemosensitivity. J Clin Oncol. 1990;8:2062-2084.
45. Meirow D, Dor J, Kaufman B, et al. Cortical fibrosis and blood-vessel damage in human ovaries exposed to chemotherapy. Potential mechanisms of ovarian injury. Hum Reprod. 2007;22:1626-1633.
46. Meirow D, Biederman H, Anderson R, Wallace H. Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol. 2010;53:727-739.
47. Fertile Hope. Risk Calculator. fertilehope.org/tool-bar/risk-calculator.cfm. Accessed June 20, 2013.
48. Newman H, Finger PT, Chin KJ, Pavlick AC. Systemic bevacizumab (Avastin) for choroidal melanoma. J Natl Cancer Inst. 2011;103:796-800.
49. Genentech, Inc. Avastin (Bevacizumab) Prescribing Information. gene.com/download/pdf/avastin_prescribing.pdf. Accessed June 20, 2013.
50. Abusief ME, Missmer SA, Ginsburg ES, et al. Ovarian response to continuing adjuvant tamoxifen (ATLAS) Collaborative Group. Long-term survival benefit of longer duration of tamoxifen compared with shorter duration among women with breast cancer at increased risk. J Natl Cancer Inst. 2005;97:1356-1367.
51. Roque M, Lattes K, Serra S, et al. Fresh embryo transfer versus frozen embryo transfer in in-vitro fertilization: a systematic review and meta-analysis. Fertil Steril. 2013;99:156-162.
52. Westphal LM, Massie JAM. Embryo and oocyte banking. In: Gracia C, Woodruff DK, eds. Oncofertility Medical Practice: Clinical Issues and Implementation. New York: Springer; 2012:51-62.
53. Sonneze M, Oktay K. Fertility preservation in female cancer patients. Hum Reprod Update. 2004;10:251-266.
54. Brinsden PR, Wada I, Tan SL, Balen A, Jacobs HS. Diagnosis, prevention and management of ovarian hyperstimulation syndrome. Br J Obstet Gynaecol. 1995;102:767-772.
55. Friedman B, Pao S, Westphal LM, Lathi RB. Oocyte retrieval following continued stimulation five days beyond ovulation yields live birth after frozen embryo transfer. J Assist Reprod Genet. 2012;29:433-435.
56. Pal L, Leykin Y, Schiffrin JL, et al. Maligancy may adversely influence the quality and behavior of oocytes. Hum Reprod. 1998;13:1857-1840.
57. Quintero RB, Helmer A, Huang JQ, Lostritto K, Oktay K. Relative potencies of anastrazole and letrozole to suppress physiological estradiol levels do not affect oocyte and embryo quality in oocyte donation cycles. Hum Reprod. 2002;17:83-87.
58. Azim AA, Constantini-Ferrando M, Lostritto K, Oktay K. Relative potencies of anastrazole and letrozole to suppress estradiol in breast cancer patients undergoing ovarian stimulation before in vitro fertilization. J Clin Endocrinol Metab. 2007;92:2197-2200.
59. Fertility Preservation using controlled ovarian hyperstimulation and cryopreservation of human oocytes and embryos. Hum Reprod Update. 2012;18:536-554.
60. Bayonas J, Westphal LM, Madrigano A, Wapnir I. Timing of breast cancer treatment with oocyte retrieval and embryo cryopreservation. J Am Coll Surg. 2009;209:603-607.
61. Madrigano A, Westphal LM, Wapnir I. Egg retrieval with cryopreservation does not delay breast cancer treatment. Am J Surg. 2007;194:477-481.
62. First baby born of frozen embryo. New York Times. April 11, 1984. Accessed from: nytimes.com/1984/04/11/us/first-baby-born-frozen-embryo.html. Accessed June 20, 2013.
63. Society for Assisted Reproductive Technology. SART 2010 National Data Summary. sartcornsonline.com rptCSR. Public MultiYear.aspx?ClinicPKID=0. Accessed June 20, 2013.
64. Chian RC, Huang JY, Tan SL, et al. Obstetrical and perinatal outcome in 200 infants conceived from vitrified oocytes. Reprod Biomed Online. 2008;6:722-729.
65. Reichman DE, Davis OK, Zaninovic N, Bex J, Terzian M, et al. Ovarian hyperstimulation syndrome (OHSS) and ectopic pregnancy after frozen embryo transfer. Fertil Steril. 2004;81:1392-1397.
66. Almog B, Azem F, Gordon D, et al. Effects of cancer on ovarian response in controlled ovarian stimulation for fertility preservation. Fertil Steril. 2012;98:957-960.
67. Pena JE, Chang PL, Chan LK, Zeitoun K, Thornton MH, Sauer MV. Supraphysiological estradiol levels do not affect oocyte and embryo quality in oocyte donation cycles. Hum Reprod. 2002;17:83-87.
68. Speroff L, Glass RH, Kase NG, eds. Clinical Gynecologic Endocrinology and Infertility. 6th ed. Philadelphi: Lippincott Williams & Wilkins; 1999:1097-1125.
69. American Childhood Cancer Organization. Childhood Cancer Statistics. acco.org/Information/AboutChildhoodCancer/ChildhoodCancerStatistics.aspx. Accessed June 20, 2013.
70. Reischman DE, Davis OK, Zaninovic N, Rosenwaks Z, Goldschad D. Fertility preservation using controlled ovarian hyperstimulation and cryopreservation in a premenarchal female with myelodysplastic syndrome. Fertil Steril. 2012;98:1225-1228.
71. Stoop D, De Vos M, Tournaye H, Devroey P. Fertility preservation utilizing controlled ovarian hyperstimulation and cryopreservation in a premenarchal girl with a history of Burkitt lymphoma. Fertil Steril. 2006;85:1029-1031.
100. SenGupta SB, Vadaparampil ST, Jadoul P, Von Langendonct A, Demylee D, Dolmans MM. Ovarian tissue cryopreservation and transplantation: a review. *Hum Reprod Update*. 2006;12:519-535.

102. Oktay K, Karlilaka G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. *N Engl J Med*. 2000;342:1919.

102. Donnez J, Dolmans MM, Demylee D, Jadoul P, Pirard C, Squifflet J. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet*. 2004;364:1405-1410.

104. Donnez J, Silber S, Andersen CY, et al. Children born after autotransplantation of cryopreserved ovarian tissue. *A review of 13 live births*. *Ann Med*. 2011;43:437-450.

105. Andersen CY, Silber SJ, Berghold SH, Jorgensen JS, Ernst E. Long-term duration of function of ovarian tissue transplants: case reports. *Reprod Biomed Online*. 2012; 25:128-132.

106. Feyereisen E, Stefanni J, Romana S, et al. Five years’ experience of preimplantation genetic diagnosis in the Parisian Center: outcome of the first 441 started cycles. *Fertil Steril*. 2007;87:60-73.

107. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancers. *Oncogene*. 2004;23:6445-6470.

108. Ethics of preimplantation genetic diagnosis for IVF. *Lancet*. 2006;7:611.

109. Smith KR, Ellington L, Chan AY, Croyle RT. Semen analysis following allogeneic bone marrow transplantation and motility in patients with early stage Hodgkin’s lymphoma enrolled in EORTC-GELA Lymphoma Group trials. *Haematologica*. 2009;94:1691-1697.

110. Fobair P, Stewart SL, Chang S, D’Onofrio BM. Spermatogenesis after luteinizing hormone-releasing hormone agonist triptorelin for treatment-induced thrombocytopenia with treatment-induced severe menorrhagia in oncology patients. *J Natl Cancer Inst*. 2006;98:1169-1176.

111. Bolour SY, Braunstein GD. Pharmacologic treatment options for hypoactive sexual desire disorder. *Womens Health (Lond Engl)*. 2005;1:253-277.

112. Bergmark K, Avall-Lundqvist E, Dickman PW, Hermingson L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med*. 1999;340:1383-1389.

113. Bober SL, Sanchez Varela V. Sexuality in adult cancer survivors: challenges and intervention. *J Clin Oncol*. 2012;30:3712-3719.

114. Krychman M, Millheiser LS. Sexual health assessment and sperm quality. *Cancer*. 2012;118:2467-2473.

115. Tal R, Botchan A, Hauser R, Yogev L, Paz G, Yavetz H. Follow-up of sperm concentration and motility in patients with lymphoma. *Hum Reprod*. 2000;15:1985-1988.

116. Anserini P, Chiodi S, Spinelli S, et al. Spermatogenesis after cancer treatment: damage and recovery. *J Natl Cancer Inst Monogr*. 2005;34:12-17.

117. Stillbirth, early death and neonatal morbidity among offspring of female cancer survivors. *Acta Oncol*. 2013;52:1152-1159.

118. Martin JA, Hamilton BE, Ventura SJ, Osterman MJK, Wilson EC, Matthews TJ. Births: final data for 2010. *Natl Vital Stat Rep*. 2012;61:1-72.

119. Ventura SJ, Hamilton BE, Sutton PD. Revised birth and fertility rates for the United States, 2000 and 2001. *Natl Vital Stat Rep*. 2003;51:1-18.

120. Williams DH, Karpman E, Sander JC, Spiess PE, Pisters LL, Lipshultz LI. Pre-treatment semen parameters in men with cancer. *J Urol*. 2009;181:736-740.

121. Del Pup L, Whipple B, Trant AS. The enhancement of female sexual function with ArginMax, a nutritional supplement, among women differing in menopausal status. *J Sex Marital Ther*. 2006;32:369-378.

122. Bolour SY, Braunstein GD. Pharmacologic treatment options for hypoactive sexual desire disorder. *Womens Health (Lond Engl)*. 2005;1:253-277.

123. Anserini P, Chiodi S, Spinelli S, et al. Spermatogenesis after cancer treatment: damage and recovery. *J Natl Cancer Inst Monogr*. 2005;34:12-17.

124. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Wilson EC, Matthews TJ. Births: final data for 2010. *Natl Vital Stat Rep*. 2012;61:1-72.

125. Davis L, Middelkoop-Eckardt L, von Hentsch H, Visser N, Sadasivan S, eds. Andrology: Male Reproductive Health and Dysfunction. New York: Springer; 2010:11-59.

126. Williams DH, Karpman E, Sander JC, Spiess PE, Pisters LL, Lipshultz LI. Pre-treatment semen parameters in men with cancer. *J Urol*. 2009;181:736-740.

127. Dada R, Gupta NP, Kucheria K. Spermatogenic arrest in men with testicular hyperthermia. *Teratog Carcinog Mutagen*. 2003; suppl 1:235-243.

128. van der Kaaai MA, Heutte N, van Echten-Arends J, et al. Spermatogenesis before treatment in patients with early stage Hodgkin’s lymphoma enrolled in EORTC-GELA Lymphoma Group trials. *Haematologica*. 2009;94:1691-1697.

129. Trost LW, Brannigan RE. Oncofertility and the male cancer patient. *Curr Treat Options Oncol*. 2012;13:146-160.

130. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental causes. *Hum Reprod*. 2001;16:972-978.

131. Matzuk MM, Lamb DJ. The biology of infertility: research advances and clinical challenges. *Nat Med*. 2008;14:1197-1213.

132. Eisenberg ML, Betts P, Herder D, Lamb DJ, Lipshultz LI. Increased risk of cancer among azoospermic men. *Fertil Steril*. 2013;100:681-685.e1.

133. Lampé H, Horwich A, Norman A, Nichols J, Dearnaley DP. Fertility and male factor infertility. In: Neischlag E, Behre HM, Nieschlag E. Physiology of testicular function during gonadotoxic chemotherapy: a systematic review and meta-analysis. *Fertil Steril*. 2011;95:694-697.

134. Marmor D, Duyck F. Male reproductive function during gonadotoxic chemotherapy: a systematic review and meta-analysis. *Fertil Steril*. 2011;95:906-914.e1-4.

135. Munster PN, Moore AP, Ismail-Khan R, et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 2012;30:533-538.

136. Meiron D, Rabinovici J, Katz D, Or R, Shutaro Y, Ben-Yehuda D. Prevention of severe menorrhagia in oncology patients with treatment-induced thrombocytopoiesis by luteinizing hormone-releasing hormone agonist and depo-medroxyprogesterone acetate. *Cancer*. 2006;107:1636-1641.

137. Loprinzi CL, Abu-Ghazaleh S, Sloan JA, et al. Phase III randomized double-blind study to evaluate the efficacy of a policarpophosphol-[119-134]bophil-based vaginal moisturizer in women with breast cancer. *J Clin Oncol*. 1997;15:969-973.

138. Del Pup L. Management of vaginal dryness and dyspareunia in estrogen sensitive cancer patients. *Gynecol Endocrinol*. 2012; 28:740-745.

139. Agarwal A, Malvezzi H, Sharma R. Effect of an isotonic lubricant on sperm collection and sperm quality. *Fertil Steril*. 2013; 99:1581-1586.

140. Fobair P, Stewart SL, Chang S, D’Onofrio C, Banks PJ, Bloom JR. Body image and sexual problems in young women with breast cancer. *Psychooncology*. 2006;15:579-594.

141. Ito TY, Polan ML, Whipple B, Trant AS. The enhancement of female sexual function with ArginMax, a nutritional supplement, among women differing in menopausal status. *J Sex Marital Ther*. 2006;32:369-378.

142. Bolour SY, Braunstein GD. Pharmacologic treatment options for hypoactive sexual desire disorder. *Womens Health (Lond Engl)*. 2005;1:253-277.

143. Bergmark K, Avall-Lundqvist E, Dickman PW, Hermingson L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med*. 1999;340:1383-1389.

144. Bober SL, Sanchez Varela V. Sexuality in adult cancer survivors: challenges and intervention. *J Clin Oncol*. 2012;30:3712-3719.

145. Krychman M, Millheiser LS. Sexual health assessment and sperm quality. *Cancer*. 2012;118:2467-2473.

146. Anserini P, Chiodi S, Spinelli S, et al. Spermatogenesis after cancer treatment: damage and recovery. *J Natl Cancer Inst Monogr*. 2005;34:12-17.
140. Trottmann M, Becker AJ, Stadler T, et al. Semen quality in men with malignant diseases before and after therapy and the role of cryopreservation. Eur Urol. 2007;52:355-367.

141. Daniell HW, Tam EW. Testicular atrophy in therapeutic orchietomy specimens from men with prostate carcinoma: association with prior prostate bed radiation and older age. Cancer. 1998;83:1174-1179.

142. Mydlo JH, Lebed B. Does brachytherapy of the prostate affect sperm quality and/or fertility in younger men? Scand J Urol Nephrol. 2004;38:221-224.

143. Hermann RM, Henkel K, Christiansen H, et al. Testicular dose and hormonal changes after radiotherapy of rectal cancer. Radiother Oncol. 2005;75:83-88.

144. Nishi Y, Hamamoto K, Fujita N, Okada S. Empty sella/pituitary atrophy and endocrine impairments as a consequence of radiation and chemotherapy in long-term survivors of childhood leukemia. Int J Hematol. 2011;94:399-402.

145. Blassin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536-2559.

146. Johnson J, Canning J, Kaneko T, Pru JK, Tilly JL. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature. 2004;428:145-150.

147. Brennemann W, Brensing KA, Leipner N, Schlegel PN. Testicular sperm extraction: a meta-analysis. Fertil Steril. 2004;80:2245-2250.

148. Boldt I, Klingmuller D. Attempted preservation from 12-18-year-old patients: a meta-analysis. Hum Reprod. 2005;20:930-936.

149. Devroey P, Liu J, Nagy Z, et al. Pregnancy after intracytoplasmic sperm injection in non-obstructive azoospermia. Clin Investig. 1999;72:838-842.

150. Jauniaux E, V得很ing-Smith C, Almeida P, Normen T, Taylor J, Grace J, Ramsay JW. Use of surgical sperm retrieval in azoospermic men: a meta-analysis. Fertil Steril. 2004;82:691-701.

151. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Hum Reprod. 1999;14:131-135.

152. Pearce S, Steinberg Z, Eggens S. Critical evaluation of modified templates and current trends in retropitoneal lymph node dissection [published online ahead of print August 2, 2013]. Curr Urol Rep.

153. Hsiao W, Devere C, Mulhall JP. Outcomes of the management of post-chemotherapy retroperitoneal lymph node dissection-associated anejaculation. BJU Int. 2012;110:1196-1200.

154. Mazzola CR, Sheinfeld J, Carver B. Ex-vivo testis sperm extraction in men undergoing orchietomy for testis cancer. J Urol. 2012;187:E802.

155. Huddart RA, Norman A, Moynihan C, et al. Fertility, gonadal and sexual function in survivors of testicular cancer. Br J Cancer. 2005;93:200-207.

156. Kiserud CE, Fossa A, Bjarot T, Holte H, Cvarncarova M, Fossa SD. Gonadal function in male patients after treatment for malignant lymphomas, with emphasis on chemotherapy. Br J Cancer. 2009;100:455-463.

157. Zaletel L, Bratanic N, Jereb B. Gonadal function in patients treated for Hodgkin’s disease in childhood. Radiol Oncol. 2010;44:187-193.

158. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med. 2006;166:1660-1665.

159. Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation. 2007;116:2694-2701.

160. Nuver J, Smit AJ, Wolfenbuttel BH, et al. The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. J Clin Oncol. 2005;23:3718-3725.

161. Gu Y, Liang X, Wu W, et al. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. J Clin Endocrinol Metab. 2009;94:1910-1915.

162. Hay CJ, Brady BM, Zitzmann M. A multicenter phase IIb study of a novel combination of intramuscular androgen (testosterone decanoate) and oral progestogen (ethinylestradiol) for male hormonal contraception. J Clin Endocrinol Metab. 2005;90:2042-2049.

163. Brackett NL, Kafetsoulis A, Ibrahim E, Aballa TC, Lynne CM. Application of 2 vibrators salvages ejaculatory failures to 1 vibrator during penile vibratory stimulation in men with spinal cord injuries. J Urol. 2007;177:660-663.

164. Schrader M, Muller M, Sofikitis N, Straub B, Krause H, Miller K. “Onco-tese”: testicular sperm extraction in azoospermic cancer patients before chemotherapy-new guidelines? Urology. 2003;61:421-425.

165. Devroey P, Liu J, Nagy Z, et al. Pregnancy after testicular sperm extraction and intracytoplasmic sperm injection in non-obsstructive azoospermia. Hum Reprod. 1995;10:1457-1460.

166. Ramsammy R, Lin K, Gosden LV, Rosenwaks Z, Palermo GD, Schlegel PN. High serum FSH levels in men with nonobstructive azoospermia does not affect success of microdissection testicular sperm extraction. Fertil Steril. 2009;92:590-593.

167. Ishikawa T, Surgical recovery of sperm in non-obstructive azoospermia. Asian J Androl. 2012;14:109-115.

168. Damani MN, Master V, Meng MV, Burgess C, Turek P, Oates RD. Postchemotherapy ejaculatory azoospermia: fatherhood with sperm from testis tissue with intracytoplasmic sperm injection. J Clin Oncol. 2002;20:930-936.

169. Hsiao W, Stahl PJ, Osterberg EC, et al. Successful treatment of postchemotherapy azoospermia with microsurgical testicular sperm extraction: the Weil Cornell experience. J Clin Oncol. 2011;29:1607-1611.

170. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancy after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet. 1992;340:17-18.

171. Chung K, Irani J, Knee G, Efymow B, Blasco L, Patrizio P. Sperm cryopreservation for male patients with cancer: an epidemiological analysis at the University of Pennsylvania. Eur J Obstet Gynecol Reprod Biol. 2004;113(suppl 1):S7-S11.

172. van Casteren NJ, van Santbrink EJ, van Inzen W, Romijn JC, Dohle GR. Use rate and assisted reproduction technologies outcome of cryopreserved semen from 629 cancer patients. Fertil Steril. 2008;90:2245-2250.

173. Meseguer M, Molina N, Garcia-Velasco JA, Remohi J, Pellcier A, Garrido N. Sperm cryopreservation in oncological patients: a 14-year follow-up study. Fertil Steril. 2006;85:640-645.

174. Kelleher S, Wishart SM, Liu PY, et al. Long-term outcomes of elective human sperm cryostorage. Hum Reprod. 2001;16:2632-2639.

175. Byrne J, Rasmussen SA, Steinhorn SC, et al. Genetic disease in offspring of long-term survivors of childhood and adolescent cancer. Am J Hum Genet. 1998;62:45-52.

176. Chow EJ, Kamineni A, Daling JR, et al. Reproductive outcomes in male childhood cancer survivors: a linked cancer-birth registry analysis. Arch Pediatr Adolesc Med. 2009;163:887-894.

177. Stahl O, Boyd HA, Giwercman A, et al. Risk of birth abnormalities in the offspring of men with a history of cancer: a cohort study using Danish and Swedish national registries. J Natl CancerInst. 2011;103:398-406.

178. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer. Fertil Steril. 2005;83:1622-1628.

179. Hirsch M, Lunenfeld B, Modan M, Ovadia J, Shemesh J. Spermarche—the age of onset of sperm emission. J Adolesc Health. 1985;6:35-39.

180. Ji CY, Ohsawa S. Onset of the release of spermatozoa (spermarche) in Chinese male youth. Am J Hum Biol. 2000;12:577-587.

181. Hagens I, Jorgensen N, Rechnitzer C, et al. Clinical and biochemical correlates of successful semen collection for cryopreservation from 12-18-year-old patients: a single-center study of 86 adolescents. Hum Reprod. 2010;25:2031-2038.

182. Hermann BP, Sukhwani M, Winkler F, et al. Spermatozonal stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm. Cell Stem Cell. 2012;11:715-726.

183. Jahnukainen K, Hou M, Petersen C, Satchell B, Soder O. In vitro transplantation of testicular cells from leuke- mic rats causes transmission of leukemia. Cancer Res. 2001;61:706-710.

184. Sato T, Katagiri K, Gohbara A, et al. In vitro production of functional sperm in cultured neonatal mouse testes. Nature. 2011;471:504-507.