Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

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Patients preparing to undergo gonadotoxic medical therapy, radiation therapy, or gonadectomy should be provided with prompt counseling regarding available options for fertility preservation for iatrogenic infertility. Fertility preservation can best be provided by comprehensive programs designed and equipped to confront the unique challenges facing these patients. This document replaces the document with a similar name, last published in 2013. (Fertil Steril® 2019;112:1022–33. ©2019 by American Society for Reproductive Medicine.)

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Over 200,000 individuals less than 49 years of age are diagnosed with cancer annually in the United States (1). Over the past 4 decades, advancements in cancer therapies, particularly chemotherapeutics, have led to dramatic improvements in survival. Given the reproductive risks of cancer therapies, in both children and those of reproductive age, and improved long-term survival, there has been growing interest in expanding the reproductive options for cancer patients (2–6). Indeed, both cancer survivors and the medical community have acknowledged the importance of patient counseling and pursuit of options for fertility preservation. As a result, various organizations have established guidelines that encourage oncology teams to offer patients referrals to reproductive specialists to discuss the implications of their cancer treatments on future reproductive capacity and to offer options for fertility preservation (7, 8). Despite increasing awareness regarding these recommendations, fertility-preservation counseling and services remain underutilized. Improved multidisciplinary collaboration between oncologists and reproductive specialists, as well as widespread availability of fertility-preservation services, are necessary to expand the reproductive options of patients facing fertility-threatening therapies (9–11).

This document summarizes programmatic requirements for comprehensive fertility-preservation care and provides specific clinical recommendations based upon currently available strategies and technologies.

PROGRAMMATIC REQUIREMENTS FOR A FERTILITY-PRESERVATION PROGRAM

Rapid Access

A single and easily identifiable contact point for referring health-care providers should be available to provide patients with rapid access to counseling programs on reproductive risks and fertility-preservation options. Clinics offering fertility preservation should have the expertise and infrastructure to provide immediate ovarian stimulation and sperm cryopreservation without delay.

Interdisciplinary Medical Team and Collaboration

Care of patients facing fertility-threatening therapies requires an interdisciplinary medical team. This team may be comprised of oncologists, reproductive endocrinologists and urologists, and reproductive surgeons trained in fertility-preservation techniques. Effective provision of fertility-preservation options requires an ongoing collaborative relationship among these specialists. Oncologists have the initial responsibility to discuss the reproductive risks of intended therapies with the patient and subsequently make urgent referrals to experienced specialists to discuss available reproductive options. A reproductive endocrinologist or urologist experienced in fertility preservation should provide patients with a timely and detailed description of appropriate fertility-preservation techniques. Ideally, referrals would be made for all adolescents and individuals of reproductive age who are planning on receiving gonadotoxic therapies. Interdisciplinary

Received September 9, 2019; accepted September 11, 2019.
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Fertility and Sterility® Vol. 112, No. 6, December 2019 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2019.09.013

communication among providers is critical to determine the optimal strategy and timing of fertility-preservation techniques, taking into consideration the overall severity and prognosis of the individual's cancer. The risks of future infertility and primary hypogonadism will vary based on the disease and treatment regimen. Additional guidance may be sought, as needed, from trained ethicists or legal counsel. If a program is unable to provide a full complement of fertility-preservation services, centers should still counsel patients about available options and provide referrals to centers with available resources.

Laboratory Requirements

Fertility-preservation programs should be associated with an experienced assisted reproductive technology (ART) program capable of providing a full complement of fertility-preservation techniques, including embryo and oocyte cryopreservation. An analogous infrastructure for cryopreservation of testicular tissue and sperm should also be available. In addition, programs should be available year-round and able to accommodate patients rapidly, counsel prepubertal patients, and ideally provide access to procedures such as cryopreservation of ovarian and testicular tissue.

Counselors

Mental-health professionals. Fertility-preservation programs should have prompt access to appropriately trained mental-health professionals to counsel patients and help them navigate what is frequently a difficult decision-making process.

Genetic counselors. Given that some diseases are heritable, a genetic counselor should be available to discuss potential risks of disease transmission to resulting offspring, and available genetic testing.

Financial counselors. Financial counseling is advised for patients seeking fertility-preservation services due to the cost and lack of medical insurance coverage for many of these techniques. Ideally, counseling regarding funding and flexible strategies for dealing with issues related to cost should be available.

MEDICAL CONSIDERATIONS

Counseling of patients pursuing fertility preservation should include a discussion of all methods of fertility preservation as well as alternatives, including future use of donor gametes, donor embryos, and adoption. The patient's current state of health must be considered, as some individuals with severely debilitating cancers may be too ill to safely undergo fertility-preservation procedures. In addition, the potential safety of future pregnancy after cancer in women should be addressed, taking into account the type of cancer and proposed treatment. The possibility of gestational surrogacy should be reviewed with all female patients, particularly those who have received or are planning on receiving pelvic radiation therapy (12, 13). Infectious disease testing, recommended by the United States Food and Drug Administration (FDA), should be considered in all patients banking reproductive tissues. See the ASRM Practice Committee document titled "Recommendations for gamete and embryo donation: a committee opinion" for recommended testing (14). In patients who elect to cryopreserve gametes, embryos, or tissues, disposition in the event of death should be discussed and documented. Because of the sensitive and urgent nature of fertility preservation, a team approach to patient counseling is recommended. If time permits, patients may meet with physicians, nurses, and mental-health professionals in order to discuss fertility-preservation options. This allows for a more comprehensive evaluation to explore and understand the psychosocial and medical needs of each patient.

CURRENTLY AVAILABLE STRATEGIES FOR FEMALES

Embryo cryopreservation

For postpubertal females who have a committed male partner or who are prepared to use donor sperm, embryo cryopreservation is an established technology that offers a predictable likelihood of success based on the number and quality of embryos stored. This process involves stimulating the ovaries with gonadotropins and surgically retrieving oocytes which are then inseminated, cultured for 2–7 days, and cryopreserved. While data on live-birth rates from banked embryos in cancer patients are limited, available data from infertile and donor populations generally are used for counseling (Table 1). For example, as can be seen in Table 1, the live-birth rate per cycle start from infertile women less than 35 years of age was 46.8% (15). If embryos are cryopreserved, a patient's future live birth prognosis may be further modified by the number and quality of the embryos or preimplantation genetic testing results when performed. These success rates decline with age. Until more data in diverse populations become available, national and clinic-specific success rates using cryopreserved embryos should be used to counsel patients regarding success rates. Patients should be thoroughly counseling about success rates given a patient's age and the number and stage of embryos cryopreserved.

Mature oocyte cryopreservation

Mature oocyte cryopreservation is another strategy for fertility preservation in postpubertal females. This process also requires ovarian stimulation and egg retrieval. Cryopreservation of oocytes rather than embryos allows for greater control of disposition of the individual's gametes in the future and also avoids issues related to embryo disposition, which may be a concern for some patients. Data on pregnancy and live birth rates from oocyte cryopreservation in cancer patients are scarce. One study found a 35% live birth rate in 80 oncofertility patients who returned to use their vitrified oocytes (16). Age at vitrification and the number of oocytes were predictors of future success (16). The current data are too limited to determine if oncofertility patients have similar outcomes to elective fertility preservation or donor oocyte patients (17, 18). However, in many patients with a high

TABLE 1

Data from 2017 live-birth rates per cycle start.

	Age range, y				
Variable	< 35	35–37	38–40	41–42	> 42
Live-birth rate/cycle start	46.8	34.4	21.0	10.1	3.1
Confidence range	46.3–47.3	33.8–35.0	20.5–21.5	9.5–10.6	2.8–3.5

ASRM. Fertility preservation before gonadotoxic therapy. Fertil Steril 2019.

likelihood of ovarian failure, oocyte vitrification represents the best option for fertility preservation and has resulted in acceptable birth rates.

In recent years, as cryopreservation and thawing techniques have been refined, mature oocyte cryopreservation in young women without a cancer diagnosis has been associated with steadily improving pregnancy rates (17, 19, 20). Randomized controlled trials of fresh vs. vitrified/warmed oocytes indicate that implantation and clinical pregnancy rates are similar (21–24). However, results from large observational studies in clinical fertility practice suggest that implantation and pregnancy rates may be lower when frozen oocytes are used compared with fresh or frozen embryos (25). As with embryo cryopreservation, pregnancy rates following oocyte cryopreservation decline with advancing age of the woman (26). It is important to recognize that success rates may not be generalizable, and clinic-specific success rates should be used to counsel patients whenever possible.

Ovarian Stimulation for Embryo or Mature Oocyte Cryopreservation

Ovarian stimulation for embryo or mature oocyte cryopreservation remains the most likely strategy to result in subsequent pregnancy. This procedure should be recommended as long as the patient's medical condition safely allows controlled ovarian stimulation (COS) with a reasonable chance of response or oocyte retrieval and if there is adequate time to carry out COS and oocyte retrieval.

Immediate or Random-Start Stimulation

Conventionally, ovarian stimulation for oocyte/embryo cryopreservation is initiated at the beginning of the follicular phase. However, this procedure may require 2–6 weeks depending on the phase of a woman's menstrual cycle at the time of presentation. In the setting of emergent fertility preservation, initiation of the stimulation should start as soon as possible regardless of phase of menstrual cycle (so-called immediate or random-start COS). Compared with conventional stimulation, immediate-start stimulations have similar embryological and pregnancy outcomes (27–29). Antagonist-based protocols, which can be performed in a similar manner as conventional starts, are recommended for immediate or random start stimulation (30). Prompt consultation and coordination of care is mandatory to facilitate initiation of treatment and avoid unnecessary delay. In the setting of a solid-tumor diagnosis and early referral, an immediate start for stimulation will result in negligible delays in cancer treatment, even in the setting of neoadjuvant chemotherapy treatment (31–33).

Some studies have suggested that stimulation and oocyte yields may be impaired in patients with cancer who have not yet received gonadotoxic therapies. A meta-analysis assessed ovarian stimulation in 227 untreated cancer patients vs. 1,258 controls from seven studies and reported a lower number of retrieved and mature oocytes (11.7 vs. 13.5 total and 9 vs. 10.8 mature, $P=.003$) (34). However, this study did not control for differences in stimulation, and studies accounting for differences in protocols have not consistently revealed differences in stimulation (19, 35). However, a comparison of oocyte yield between those diagnosed with cancer and women undergoing elective fertility preservation showed no difference in outcomes (36); this study was a suitable comparison, as both groups of patients were not presented as infertile.

Because women typically have time to pursue only a single cycle of in vitro fertilization (IVF) prior to gonadotoxic therapy, it is important to procure a sufficient number of oocytes to maximize the chance of a successful future pregnancy (18). However, the risks of overstimulation and ovarian hyperstimulation syndrome (OHSS) need to be considered. The impact of OHSS can be profound in a cancer patient, since this syndrome has the potential to delay and complicate planned lifesaving cancer therapy. Therefore, the use of appropriate strategies to reduce the risk of OHSS may be particularly valuable for young cancer patients undergoing ovarian stimulation (37). Strategies that may be utilized to reduce the risk of OHSS include gonadotropin-releasing hormone (GnRH) antagonist protocols with GnRH agonists to trigger the final maturation of oocytes (38, 39). Other risks associated with ovarian stimulation in cancer patients may include delay of cancer therapy, theoretic stimulation of estrogen-sensitive cancers, and a risk of thromboembolic phenomena. Although there are limited studies evaluating the safety of ovarian stimulation, there have been a few observational studies in breast cancer patients with over 10 years of follow-up that suggest no change in disease-free survival (40–42). In these studies, tamoxifen or letrozole were used during the stimulation. One limited study also compared the impact of ovarian stimulation on patients undergoing neoadjuvant chemotherapy before tumor resection and found similar outcomes in pathologic clinical response (32).

While oocytes for cryopreservation ideally should be procured prior to exposure to cancer therapies, this may not always be possible due to the patient's medical condition. There are no human studies that have specifically examined the quality of oocytes and embryos that result following a prior course of chemotherapy. It is known that chemotherapeutic agents can cause DNA abnormalities as well as oxidative damage in somatic and germ cells (43, 44). In mice, conceptions that occurred within 3 months of exposure to cyclophosphamide resulted in a higher rate of pregnancy failures and fetal malformations (45). However, studies that have examined pregnancy outcomes in cancer survivors remote from therapy have found no significant increase in congenital malformations, genetic abnormalities, or malignant neoplasms in the resulting offspring (13, 46–48). A safe interval between completion of chemotherapy and oocyte or embryo cryopreservation has not been established.

Ovarian Tissue Cryopreservation

Ovarian tissue banking is an acceptable fertility-preservation technique and is no longer considered experimental. Ovarian tissue banking is the only method to preserve fertility for prepubertal girls since ovarian stimulation and IVF are not options (49, 50). Cryopreservation of ovarian cortical tissue theoretically represents an efficient way of preserving thousands of ovarian follicles at one time. This technique has been proposed principally for prepubertal females and for those who cannot delay cancer treatment in order to undergo ovarian stimulation and oocyte retrieval.

Ovarian tissue cryopreservation involves obtaining ovarian cortical tissue prior to ovarian failure by laparoscopy or laparotomy, dissecting the tissue into small fragments, and cryopreserving it using either a slow-cool technique or vitrification. Orthotopic transplantation has been the most successful method for using ovarian tissue in humans. As of 2017, there have been over 130 live births reported after orthotopic transplantation of previously cryopreserved and thawed ovarian tissue (49, 51–62) This technique has been successful in patients with a variety of malignant and nonmalignant conditions facing gonadotoxic therapies. While the denominator of transplants is not known, pregnancy and live-birth rates have been reported by specific centers and networks. For example, the pregnancy rate was reported to be 29% and live-birth rate 23% in 111 patients who underwent transplant by a network of five major European centers (63). Similarly, pregnancy and live-birth rates were 33% and 25%, respectively, in another report (64). A live birth has been reported in a female who cryopreserved tissue before menarche (live birth after autograft of ovarian tissue cryopreserved during childhood) (65). It has been observed that ovarian function generally resumes between 60–240 days post-transplant and lasts for up to 7 years (66, 67). It is unlikely that ovarian tissue transplantation is effective for preservation of long-term endocrine function and generally should be performed to promote fertility when patients are ready to conceive. Only one human live birth has been reported after heterotopic transplantation (68).

As there is a relatively low follicular survival rate following ovarian transplantation, it does not appear to be feasible to cryopreserve ovarian tissue from women older than 40 years of age (53). In patients younger than 40 years, the amount of ovarian tissue cryopreserved theoretically should be proportional to the risk of age-related diminished follicular reserve. Based on current evidence, removal of both ovaries for cryopreservation is not justified at this time unless the chemotherapy regimen has an extremely high likelihood of inducing complete ovarian failure.

There is a legitimate concern regarding the potential for reseeding tumor cells following ovarian tissue cryopreservation and transplantation procedures in cancer patients. Although many types of cancer virtually never metastasize to the ovaries, leukemias are systemic in nature and therefore pose a significant risk (69). Therefore, autologous transplantation is contraindicated in situations where cancer cells may be present in cryopreserved ovarian tissue. It is unclear whether screening with histologic evaluation or with tumor markers is reliable and reduces the risk of reseeding tumor cells (70).

As of 2018, one live birth has been reported after autologous transplantation of tissue in a patient with leukemia after screening the tissue by performing xenotransplantation in a severe combined immunodeficiency (SCID) mouse (71). Prior to undertaking ovarian tissue cryopreservation, a consultation with the patient's medical oncologist is appropriate to understand potential risks related to transplantation (72, 73).

In order to avoid future transplantation of tissue, it would be ideal to isolate and mature oocytes from ovarian tissue for use in IVF. Reports suggest that intraoperative recovery of immature oocytes from ovarian tissue can be followed by in vitro maturation (IVM) and subsequent cryopreservation of either mature oocytes or embryos (74, 75). This approach requires a high degree of collaboration among surgeons and an appropriately trained laboratory staff (76). In addition, basic laboratory research is being conducted to develop methods for isolating and maturing oocytes and follicles of all stages of maturation from previously cryopreserved cortical tissue. To date, this approach has led to live births only in animal models (77).

Overall, data on the efficacy, safety, and reproductive outcomes after ovarian tissue cryopreservation are still limited. Given the current body of literature, ovarian tissue cryopreservation should be considered an established medical procedure with limited effectiveness that should be offered to carefully selected patients. Ovarian tissue transplantation can be technically challenging and should be offered only by centers with the necessary laboratory and surgical expertise.

Ovarian Suppression with GnRH Analogs

Several randomized trials and meta-analyses have explored the benefits of GnRH analogs during chemotherapy (78–89). However, the use of GnRH analogs for ovarian protection during chemotherapy remains controversial. While two RCTs demonstrated that menstrual function, ovulation, and pregnancy were more likely to occur in breast cancer

patients following co-treatment with GnRH agonists during chemotherapy compared with those who did not receive this therapy, benefits in terms of fertility outcomes are lacking (81, 83, 84). Studies have been limited by inadequate follow-up and the assessment of surrogate measures of fertility rather than pregnancy rates. While GnRH analogs are not currently FDA approved for fertility preservation, these medications may be used "off label." Given the evidence of efficacy, GnRH agonists may be offered to breast cancer patients to reduce the risk of premature ovarian insufficiency (89), but should not be used in place of other fertility preservation alternatives (8). Further studies are required to establish the efficacy of this treatment and to determine which patients are the best candidates for its use. Nonetheless, this therapy may help to prevent heavy bleeding in patients with thrombocytopenia related to chemotherapy and stem-cell transplantation and should be considered in such patients (90).

Ovarian Transposition

Patients requiring local pelvic radiation treatment may benefit from transposition of the ovaries to sites away from maximal radiation exposure (8, 91–93). Ovarian transposition may be accomplished at the time of initial oncologic surgery or at a later time. It is important to recognize that this procedure may preclude future transvaginal oocyte retrieval if IVF is required. Transabdominal retrieval may be accomplished in some patients (94).

Conservative Treatments for Reproductive Malignancies

Patients undergoing surgery for cervical, endometrial, or ovarian cancer or borderline tumors of the ovary may be candidates for conservative surgical approaches or, in the case of endometrial disease, initial medical therapy. Patients should discuss treatment options with a gynecologic oncologist.

SPECIAL CLINICAL CONSIDERATIONS FOR FEMALE PATIENTS

Breast Cancer

Patients with breast cancer undergoing initial treatment with lumpectomy or mastectomy often will have an interval of time available for an oocyte retrieval prior to initiating postoperative chemotherapy (95). Nevertheless, these patients present a particular challenge because of concerns regarding the potential impact of ovarian stimulation hyperestrogenemia on the course of their disease. Thorough counseling by a qualified clinician is mandatory in these cases. While standard ovarian stimulation (employing injectable gonadotropins) is a reasonable choice, providers may wish to offer treatment incorporating co-administration of aromatase inhibitors to decrease circulating estrogen levels or tamoxifen as an estrogen-receptor blocker (40–42). Breast cancer patients who are not comfortable with the potential impact of COS on their disease or who lack sufficient time to undergo oocyte retrieval may be candidates for IVM or ovarian tissue-preservation protocols.

BRCA Mutations

Carriers of BRCA mutations may be offered bilateral salpingo-oophorectomy (BSO) as a risk-reduction strategy for ovarian cancer (96). Ideally, BSO is performed after childbearing is complete. However, these patients may be candidates for either embryo or oocyte cryopreservation and ordinarily are faced with time frames that may permit multiple oocyte retrievals. They also may be candidates for preimplantation genetic testing of BRCA mutations prior to embryo transfer. Genetic counseling is recommended for all these patients.

Ovarian tissue cryopreservation for transplantation is not advisable in patients carrying a BRCA mutation given the increased risk of ovarian cancer in this population. However, at the time of oophorectomy, these patients may consider ovarian tissue harvesting for IVM of oocytes or follicles. The experimental nature of this technique should be discussed with patients, as well as the fact that this approach has not led to live births to date. In addition, there is concern that cryopreserving ovarian tissue may prevent thorough pathologic examination of the ovaries and therefore may limit the diagnosis of an occult epithelial malignancy.

Gynecologic Malignancies

The management of young women with localized gynecologic cancer can be complex and challenging. Patients and physicians must balance the choice of following long-established surgical guidelines versus the desire to maintain reproductive function and avoid surgical menopause. Many of these women will undergo surgical treatment to remove some or all of their reproductive organs. Ideally, a reproductive specialist should see these patients prior to treatment. Early-stage disease should be eligible for procedures that preserve reproductive potential by way of fertility sparing surgery, oophoropexy, and/or egg/embryo cryopreservation. The success depends on the diagnosis and treatment (97–100). If a hysterectomy is performed, these patients should be counseled regarding surrogacy.

Hematologic malignancies

Patients with hematologic disorders present unique challenges to fertility-preservation counseling and management. Often, these individuals are too ill at diagnosis to be eligible for fertility-preservation procedures that typically require a delay in therapy of days to weeks and involve minor surgical procedures that pose increased risks in patients with abnormal hematologic parameters. Moreover, even if leukemic patients are eligible for ovarian tissue cryopreservation, there is concern about reseeding malignant cells with future autologous transplantation of tissue (69, 70, 101). While patients with lymphoma are better candidates for fertility-preservation techniques, initial therapies do not have a substantial risk of gonadotoxicity; therefore, there is less motivation to pursue fertility-preservation methods. For these reasons, patients with hematologic malignancies often present for fertility-preservation consultation only after induction chemotherapy or a relapse in disease has been diagnosed and sterilizing stem-cell transplantation has been

recommended. Hence, individuals with hematologic malignancies often present after having been exposed to gonadotoxic therapies (102). While these patients may be candidates for ovarian stimulation for oocyte or embryo cryopreservation (103), pregnancy outcomes using embryos created after recent exposure to chemotherapy are not known. Animal data suggest that there may be an increased risk of miscarriage and birth defects (45).

In addition, patients with abnormal hematologic parameters may be at risk for surgical complications. Particular attention should be paid to patients' hematological parameters to assure that the selected approach is safe. Patients with leukemia may be good candidates for GnRH agonist co-administration in order to manage ovulation and menstrual bleeding during chemotherapy, given that fertility-preservation options are limited.

Children and Adolescents

Children and adolescents represent a special patient group that must be approached thoughtfully. Unfortunately, several factors hamper fertility preservation in these patients, including lack of available fertility-preservation programs at pediatric health-care facilities, lack of knowledge of the vulnerability of these individuals to cancer therapies, and discomfort in discussing reproductive health issues with these patients and their parents.

Fertility preservation in this special group of patients is nonetheless possible. Postpubertal girls under the age of 18 may be candidates for ovarian stimulation for mature oocyte cryopreservation. This also may be an option for adolescent females who are peripubertal but still premenarchal (104). IVM and ovarian tissue cryopreservation also may be offered to this population. Ovarian tissue cryopreservation is currently the only way to cryopreserve gametes in prepubertal girls. Working with these individuals and their parents requires an approach that is sensitive to various levels of physical and psychological development. Close collaboration among primary physicians, reproductive endocrinologists, mental-health professionals, and ethicists is particularly helpful. Given that this is a particularly vulnerable population, careful counseling and informed consent are especially recommended.

CURRENTLY AVAILABLE STRATEGIES FOR MALES

Ejaculated Sperm Cryopreservation

Counseling all males about the reproductive risks of cancer treatment and availability of fertility preservation options prior to initiation of cancer therapy and consideration of referral to a reproductive urologist is recommended. Postpubertal males should be offered sperm cryopreservation as this is the standard fertility-preservation method. Semen collection by masturbation is feasible and successful in the majority of adult and postpubertal male patients with cancer. Semen collection should be performed prior to the administration of gonadotoxic therapies such as chemotherapy or radiation therapy. Ideally, at least two to three ejaculated samples should be obtained to provide adequate numbers of sperm sufficient to yield several vials for cryopreservation. Males who cryopreserve sperm should be counseled about the quality of the cryopreservation sample and potential for future use.

It also is important to recognize that men with cancer may have underlying impairment in semen parameters prior to the administration of any oncologic therapy (105, 106). Several factors associated with cancer can negatively impact male reproductive potential, including disruption of the normal hypothalamic-pituitary-gonadal axis and injury to the germinal epithelium as a result of cytotoxic immune response to cancer, fever, and malnutrition.

Some men, especially young teenagers, may be unable to ejaculate by masturbation. Counseling and a comfortable environment to collect may be helpful (107). Pubertal status as well as a variety of factors related to cancer can contribute to this condition, including anxiety, fatigue, hypogonadism, pain, comorbidities such as diabetes, neurologic problems, and side effects from a variety of medications such as opioids and antidepressants, as well as the underlying disease itself. For these young men or for men who are unable to ejaculate, the following therapeutic options can be considered to obtain ejaculated sperm for cryopreservation:

Use of phosphodiesterase type 5 (PDE-5) inhibitors. While these oral agents are classically used to treat erectile dysfunction, they have been utilized with success for men experiencing difficulty providing semen samples for use in assisted reproductive techniques (108). The patient should be evaluated and counseled regarding contraindications, timing of administration, need for sexual stimulation, and side effects prior to prescribing these agents.

Vibratory stimulation. Penile vibratory stimulation may be used to induce ejaculation for men with neurologic injuries or other factors negatively impacting the ejaculatory reflex, including psychogenic anejaculation (109). These devices provide increased penile stimulatory input and can help trigger the ejaculatory reflex in many men otherwise unable to reach climax by sexual intercourse or masturbation (110). While it typically does not work as well for men with intact spinal cords, it may be tried prior to more invasive procedures.

Electroejaculation. For those men and peri-pubertal males who are non-responsive to penile vibratory stimulation, electroejaculation may be offered as an alternative (111, 112). The non-specific stimulation of pelvic tissues including the prostate and seminal vesicles via a transrectal probe may lead to seminal emission (113). Electroejaculation must be conducted under anesthesia, unless the patient also has complete loss of sensation below the umbilicus (for example, a spinal cord injury).

Retrograde ejaculation. Some men suffer from retrograde ejaculation, which may result from prior surgery (autonomic or pelvic nerve injury, bladder neck injury, etc.). Alpha-agonists such as pseudoephedrine can be used with care in some of these men to restore antegrade ejaculation (114).

For those men who are not candidates for alpha-agonists, as well as those men who don't respond to this therapy, collection and processing of the urine after ejaculation can lead to isolation of viable sperm for cryopreservation (114). Numerous protocols for this process are available. They generally include medical urinary alkalization with or without instillation of sperm wash media into the bladder just prior to ejaculation.

Cryopreservation of surgically extracted sperm

Surgical sperm extraction is an alternative strategy for males who cannot ejaculate via the aforementioned techniques, or who have azoospermia or insufficient sperm in the ejaculate to freeze (115). For most males undergoing surgical sperm retrieval for fertility preservation purposes, testicular sperm retrieval will yield the best results. The testicular tissue containing sperm is processed and cryopreserved shortly after the procedure. The sample can be subsequently thawed, and sperm can be isolated and utilized for IVF/intracytoplasmic sperm injection (ICSI) at a later time. Testicular sperm extraction is typically performed in the operating room as an outpatient procedure, and consideration should be given to scheduling concurrently with other procedures, such as placement of a central venous access device.

GnRH analog therapy in men

GnRH analogs have been used to suppress the hypothalamic-pituitary-gonadal axis during chemotherapy administration in an effort to protect the germinal epithelium (116). Although animal studies revealed promising results, human studies failed to demonstrate fertility preservation or more rapid return of spermatogenesis after chemotherapy. It is, therefore, not appropriate to use in males for fertility preservation.

Cryopreservation of testicular tissue in prepubertal boys

Testicular tissue cryopreservation is the only method to preserve the fertility of prepubertal boys who are not yet producing sperm or for pubertal patients who cannot or will not produce a semen sample. If sperm are observed on intraoperative analysis of testis biopsies from pubertal patients, those samples can be cryopreserved similar to how TESE samples are processed (117, 118). For prepubertal boys, testicular tissue extraction in an effort to preserve future fertility is considered investigational at the time of publication and should be pursued under the auspices of a clinical trial. If tissues are immature and no sperm are recovered, immature testicular tissue can be cryopreserved. There are several cell- and tissue-based technologies in the research pipeline that may allow patients to use their cryopreserved testicular tissues in the future to produce sperm (119–123). Those technologies rely on the activity of spermatogonial stem cells that are present in the tissues of young patients (124) and poised to initiate sperm production at puberty (125, 126).

Testicular tissue cryopreservation usually involves the removal of testicular tissue by open biopsy of one testis and should occur before the initiation of gonadotoxic therapy. Most centers cut the biopsied testicular tissues into small pieces (1-25 mm3) and freeze at a controlled slow rate (117, 127–131). Freezing intact pieces of testicular tissue preserves the options for cell-based or tissue-based therapies in the future (120). Testicular biopsy in young patients is generally considered safe with no reported long-term impacts on testicular anatomy, growth or hormonal function (117, 127–129, 132).

Spermatogonial stem cell transplantation and testicular tissue grafting are mature technologies that have produced fertilization competent sperm and embryos or offspring in numerous mammalian species, including nonhuman primates (133–142). Autologous transplantation of frozen and thawed testis cells in seven survivors of non-Hodgkin's lymphoma was reported in 2003 (143), but the outcomes of those procedures were not reported. Autologous transplantation of cryopreserved testicular cells or tissues may not be appropriate for patients with blood-borne cancers or testicular cancers due to the risk of re-seeding tumor cells. For those cases, testicular tissue/cell xenografting or testicular tissue organ culture are experimental options that may allow production of sperm outside the body of the patient survivor (141, 144–150).

In summary, animal research demonstrates the feasibility and safety of next generation reproductive technologies using frozen and thawed testicular tissues. No human live births have been reported using those technologies, so immature testicular tissue cryopreservation should be considered experimental and offered only to patients who are prepubertal, at significant risk of infertility due to their disease or medical treatment (151), and as part of a clinical trial. However, the promising results in animals, combined with >15 years of experience cryopreserving immature testicular tissues for young patients (117, 123, 127, 129, 131, 132, 152–155), support the continued development of methods to preserve the fertility of males (121).

SPECIAL CLINICAL CONSIDERATIONS FOR MALE PATIENTS

Testicular Cancer

Men suspected of having testicular cancer can be offered sperm cryopreservation prior to orchiectomy (156). This is an especially important consideration for men with a solitary testis or contralateral testicular atrophy. Some of these men will be found to have azoospermia or severely impaired semen parameters that may jeopardize fertility-preservation efforts (157). For these patients, sperm extraction from the affected testis immediately after orchiectomy on a sterile "back bench" has been successfully utilized. This procedure has been referred to as "onco-TESE" in the literature; this testicular tissue may represent the only source of viable sperm for cryopreservation in some patients (158, 159).

SUMMARY

- Patients facing treatments likely to impair reproductive function deserve prompt counseling regarding their

options for fertility preservation and rapid referral to an appropriate program.

- Embryo, oocyte, and ejaculated or testicular sperm cryopreservation remain the principle established modalities for fertility preservation.
- Ovarian tissue cryopreservation is no longer considered experimental and can be used in prepubertal patients or when there is not time for ovarian stimulation.
- Testicular tissue cryopreservation in prepubertal males is still considered experimental and should be conducted under research protocols when no other options are feasible.
- GnRH agonists can be offered to women with breast cancer and potentially other cancers for the purpose of protection from ovarian insufficiency. However, GnRH analogs should not replace oocyte or embryo cryopreservation as the established modalities for fertility preservation.
- GnRH agonist therapy is not effective in preserving fertility in men and is not recommended.
- Ovarian transposition may be offered to women undergoing pelvic radiation.

Acknowledgments: This report was developed under the direction of the Practice Committees of the American Society for Reproductive Medicine (ASRM) and the Society for Reproductive Endocrinology and Infertility (SREI) as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committees of ASRM and SREI and the Board of Directors of ASRM have approved this report.

This document was reviewed by ASRM members and their input was considered in the preparation of the final document. The Practice Committee acknowledges the special contribution of Ralph Kazer, M.D., in the preparation of this document. The following members of the ASRM Practice Committee participated in the development of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationship disclosed did not participate in the discussion or development of this document.

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