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

The Practice Committee of the American Society for Reproductive Medicine

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Patients preparing to undergo gonadotoxic medical therapy or radiation therapy or gonadectomy should be provided with prompt counseling regarding available options for fertility preservation. Fertility preservation can best be provided by comprehensive programs designed and equipped to confront the unique challenges facing these patients. (Fertil Steril® 2013;100:1214–23. ©2013 by American Society for Reproductive Medicine.)

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Over 100,000 individuals less than 45 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 and improved long-term survival, there has been growing interest in expanding the reproductive options for cancer patients. Indeed, both cancer survivors and the medical community have acknowledged the importance of patient counseling and pursuit of options for fertility preservation. In 2006, the American Society of Clinical Oncology first published recommendations on fertility preservation, stating that "As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility-preservation options or refer patients to reproductive specialists" (2). Despite increasing awareness regarding these recommendations, fertility-preservation services are 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 (3–5).

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, easily identifiable contact point for referring health care providers or patients should be available in order to provide patients rapid access to a program offering fertility-preservation services.

Interdisciplinary Medical Team

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.

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 also should be provided. In addition, programs should be able to accommodate patients rapidly and be available year round. Ideally, programs also should be able to counsel prepubertal patients and provide access to procedures (under institutional review board [IRB]-approved protocols) such as ovarian

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and testicular tissue cryopreservation, both of which are still considered experimental.

Counselors

Mental health professionals. Fertility-preservation programs also 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 any potential risks of transmission of the disease to the 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 available funding and flexible strategies for dealing with issues relating to cost should be provided.

Interdisciplinary Collaboration

Effective provision of fertility-preservation options requires an ongoing collaborative relationship among medical and surgical oncologists, reproductive endocrinologists, and urologists. Oncologists have the initial responsibility to discuss the reproductive risks of intended therapies with the patient and subsequently make referrals to experienced specialists to discuss available reproductive options. A detailed description of appropriate fertility-preservation techniques should be provided by a reproductive endocrinologist or urologist experienced in that field. Ideally, referrals would be made for all adolescents and individuals of reproductive age who are planning on receiving gonadotoxic therapies. Interdisciplinary 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. Additional guidance may be sought, as needed, from trained ethicists or legal counsel.

Medical Considerations

Counseling of patients pursuing fertility preservation should include a discussion of all methods of fertility preservation as well as alternatives, such as the 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 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 (6, 7). US Food and Drug Administration (FDA) infectious disease testing should be considered in all patients banking reproductive tissues. See the ASRM Practice Committee document titled "Recommendations for Gamete and Embryo Donation" for recommended testing (8). 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. Ideally, if time permits, patients should meet with physicians, nurses, and mental health professionals over several visits 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

Female

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 provides a predictable likelihood of success based on the number and quality of embryos stored. While data on the 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, live birth rate per embryo transfer from embryos thawed from infertile women less than 35 years of age was 38.7% and 34.8% for thawed oocyte donor cycles (9). These success rates are lower than those reported for fresh embryo transfer cycles and decline with age. National and clinic-specific success rates using cryopreserved embryos should be used to counsel patients regarding success rates.

Mature oocyte cryopreservation. Mature oocyte cryopreservation is a strategy for fertility preservation in postpubertal females without a committed male partner and who do not wish to use donor sperm. In addition, cryopreservation of oocytes rather than embryos allows for greater control of disposition of the individual's gametes in the future. This process, which is no longer considered experimental (10), involves stimulating the ovaries with gonadotropins and surgically retrieving mature oocytes. Freezing oocytes, rather than embryos, also avoids considerations of embryo storage and disposal, which may be a concern for some patients. Data on pregnancy and live birth rates from oocyte cryopreservation in cancer patients are scarce and until such data are

TABLE 1

Data from 2010 SART statistics (146,693 cycles).

	Oocyte donors	< 35	35–37	38–40	41–42	> 42
Fresh cycle, live birth/ET	55.6	47.8	38.4	28.1	16.8	6.3
Thawed, live birth/ET	34.8	38.7	35.1	28.5	21.4	15.3
Average no. ET	2.0	1.9	1.9	2.1	2.2	2.1

Note: ET = embryo transfer.

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available, success rates must be extrapolated from other populations, such as young oocyte donors (10), for patient counseling.

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 (10–12). Four randomized controlled trials of fresh vs. vitrified/warmed oocytes indicate that implantation and clinical pregnancy rates are similar (Table 2) (13–16). 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 (17). As with embryo cryopreservation, pregnancy rates following oocyte cryopreservation decline with advancing age of the woman (18). 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. The process of ovarian stimulation and oocyte retrieval for obtaining mature oocytes is similar to the process of obtaining mature oocytes for embryo cryopreservation.

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 does not preclude safely carrying out controlled ovarian stimulation (COS) or oocyte retrieval, the patient has a reasonable chance of responding to COS, and adequate time is available to undergo COS and carry out oocyte retrieval. Given that the phase of the menstrual cycle is a major consideration in starting ovarian stimulation, prompt consultation and coordination of care is mandatory to facilitate initiation of treatment and avoid unnecessary delay.

Some studies have suggested that stimulation and oocyte yields may be impaired in patients with cancer who have not yet received gonadotoxic therapies. A recent meta-analysis assessed ovarian stimulation in 227 untreated cancer patients vs. 1,258 controls from 7 studies and reported a lower number of retrieved and mature oocytes (11.7 vs. 13.5 total and 9 vs. 10.8 mature, $P=.003$) (19). However, this study did not control for differences in stimulation, and studies accounting for differences in response to stimulation protocols have not consistently revealed differences in stimulation (11, 20). In women who have undergone prior gonadotoxic therapy, measures of ovarian reserve may be compromised and ovarian stimulation may be impaired (21). Counseling regarding expected success rates may be difficult in such patients.

Selecting the appropriate ovarian stimulation regimen can be challenging in patients pursuing fertility preservation because response to ovarian stimulation can be unpredictable

TABLE 2

Summary of randomized controlled trials comparing fresh vs. vitrified oocytes.

	Cobo 2008 (13)	Cobo 2010 (14)	Rienzi 2010 (15)	Parmegiani 2011 (16)
Patient population	**Oocyte donors**	**Oocyte donors**	**Infertile patients < 43 years of age requiring ICSI with > 6 mature oocytes**	**Infertile patients <42 years of age requiring ICSI with >5 mature oocytes**
No. patients				
Vitrification	30	295	40	31
Fresh	30	289	40	31
Mean age at retrieval (y)	26	26	35	35
No. oocytes				
Vitrification	231	3,286	124	168
Fresh	219	3,185	120	NA
No. oocytes per retrieval	18.2	11	13	NA
Survival (%)	96.9	92.5	96.8	89.9
Fertilization rate (%)				
Vitrification	76.3	74	79.2	71
Fresh	82.2	73	83.3	72.6
No. transferred, vitrification vs. fresh				
Vitrification	3.8	1.7	2.3	2.5
Fresh	3.9	1.7	2.5	2.6
Day of transfer	3	3	2	2–3
Implantation rate (%)				
Vitrification	40.8	39.9	20.4	17.1
Fresh	100	40.9	21.7	NA
CPR/transfer vitrification vs. fresh				
Vitrification	60.8 (23 transfers)	55.4	38.5	35.5
Fresh	100 (1 fresh transfer)	55.6	43.5	13.3
CPR, oocyte thawed (%)	6.1	4.5	12	6.5

Note: All used vitrification with Cryotop, 15% ethylene glycol + 15% dimethyl sulfoxide + 0.5M sucrose. CPR = clinical pregnancy rate; ICSI = intracytoplasmic sperm injection; NA = not applicable.

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and the need to initiate cancer therapy may limit performing a second cycle. Assessing ovarian reserve with serum follicle-stimulating hormone (FSH), antral follicle count, and/or anti-müllerian hormone (AMH) may be useful to estimate the optimal gonadotropin dose, though none of these measures has been shown to be predictive of failure to conceive (22). Gonadotropin-releasing hormone (GnRH) antagonist protocols may afford more flexibility than other protocols. Initiation of ovarian stimulation at any time during the menstrual cycle, including luteal starts, has been reported to be successful (23–26). 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 pregnancy in the future. However, the risks of overstimulation and ovarian hyperstimulation syndrome (OHSS) also 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 (27). Strategies that may be utilized to reduce the risk of OHSS include GnRH antagonist protocols with GnRH agonists to trigger the final maturation of oocytes (23). 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.

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 (28, 29). In mice, conceptions that occurred within 3 months of exposure to cyclophosphamide resulted in a higher rate of pregnancy failures and fetal malformations (30). 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 (7, 31, 32). Live birth rates from pregnancies in cancer survivors are similar to those of siblings (33). However, a safe interval after completing chemotherapy prior to oocyte or embryo cryopreservation has not been established.

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.

Ovarian transposition. Patients requiring local pelvic radiation treatment may benefit from transposition of the ovaries to sites away from maximal radiation exposure (34–36). This may be accomplished at the time of initial oncologic surgery or at a later time. It is important to recognize that ovarian transposition may preclude future transvaginal oocyte retrieval if in vitro fertilization is required. Transabdominal retrieval may be accomplished in some patients (37).

Investigational

The following approaches still should be considered experimental:

Ovarian tissue cryopreservation. 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 banking may be the only acceptable method to preserve fertility for prepubertal girls since ovarian stimulation and IVF are not options (38, 39).

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. While heterotopic transplantation and IVF have led to live births in animals, this technology had not resulted in a live human birth as of April 2013 (40). Orthotopic transplantation has been more successful in humans and a number of case reports have described successful pregnancies after orthotopic transplantation of previously cryopreserved and thawed ovarian tissue (38, 41–52) (Table 3). This technique has been successful in patients with a variety of malignant and nonmalignant conditions facing gonadotoxic therapies. Importantly, no live births have been reported in females who cryopreserved tissue before puberty. It has been observed that ovarian function generally resumes between 60–240 days post-transplant and lasts for up to 7 years (53, 54). Therefore, it is unlikely that ovarian tissue transplantation is effective for preservation of long-term endocrine function and only should be performed in order to promote fertility when patients are ready to conceive.

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 (43). 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 the 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 (55). Therefore, autologous transplantation is contraindicated in situations where cancer cells may be present in the cryopreserved ovarian tissue. It is unclear whether screening with histologic evaluation or

TABLE 3

Summary of reported live births after orthotopic transplantation of previously cryopreserved ovarian tissue (as of August 2012).

Disease	Age at cryopreservation (y)	Surgical method	Chemotherapy before cryopreservation	Pregnancy	Reference
Hodgkin lymphoma	25	Ovarian biopsy	No	Spontaneous live birth	(44)
Neuro-ectodermic tumor	19	Ovarian biopsy	No	Spontaneous live birth	(45)
Hodgkin lymphoma	20	Ovarian biopsy	No	Spontaneous live birth	(42)
Non-Hodgkin lymphoma	28	Ovarian biopsy	Yes	IVF, live birth	(46)
Hodgkin lymphoma	24	Unilateral oophorectomy	Yes	2 spontaneous live births	(47)
Microscopic polyangiitis	27	Unilateral oophorectomy	Yes	IVF, live birth	(43)
Breast cancer	36	Ovarian biopsy	No	IVF, 2 live births (twins)	(48)
Premature ovarian failure	24	Ovarian biopsy	No	Spontaneous live birth	(38)
Hodgkin lymphoma	27	Unilateral oophorectomy	Yes	IVF, live birth	(49)
Ewing sarcoma	27	Unilateral oophorectomy	No	IVF, 2 live births	(49)
Sickle cell	20	Unilateral oophorectomy	No	Spontaneous live birth	(50)
Hodgkin lymphoma	25	Ovarian biopsy	Yes	Spontaneous live birth	(51)
Thalassemia	19	Unilateral oophorectomy	No	IVF, live birth	(52)

Practice Committee. Fertility preservation for cancer. Fertil Steril 2013.

with tumor markers is reliable and reduces the risk of reseeding tumor cells (56). Prior to undertaking ovarian tissue cryopreservation, a consultation with the patient's medical oncologist is appropriate (57, 58).

In order to avoid future transplantation of tissue, it would be ideal to be able 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 and subsequent cryopreservation of either mature oocytes or embryos (59, 60). However, no live births have been reported from this technique. This approach requires a high degree of collaboration between surgeons and an appropriately trained laboratory staff (61). 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 (62).

Overall, there are still insufficient data on the efficacy, safety, and reproductive outcomes after ovarian tissue cryopreservation to consider this option an established technology. Currently, ovarian tissue cryopreservation can be recommended only as an experimental protocol in carefully selected patients. Ovarian tissue transplantation can be technically challenging and should be offered only by centers with the necessary laboratory and surgical expertise.

Transvaginal retrieval of immature oocytes with in vitro maturation (IVM) of oocytes. Transvaginal retrieval of immature oocytes with in vitro maturation (IVM) of oocytes has been advocated for patients with estrogen-sensitive tumors and for those who require urgent initiation of cancer therapy. This approach involves the retrieval of immature oocytes in unstimulated postpubertal ovaries and then maturation of the oocytes in the laboratory (IVM) for mature oocyte or embryo cryopreservation. While several live births have been reported using this technique, this technique still should be considered investigational because the efficacy and safety are unknown (63–65).

Ovarian suppression with GnRH analogs. The use of GnRH analogs for ovarian protection during chemotherapy remains controversial. While several reports suggest that menstrual function and ovulation may be more likely to occur in 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 (66–68). 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." Further studies are required to establish the efficacy of this treatment and 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 (69).

SPECIAL CLINICAL CONSIDERATIONS

Female Patients

Breast cancer. Patients with breast cancer undergoing initial treatment with lumpectomy or mastectomy often will have an interval of time available to them for an oocyte retrieval prior to initiating postoperative chemotherapy (70). Nevertheless, they present a particular challenge because of concerns regarding the potential impact of COS-related hyperestrogenemia on the course of their disease. Once again, thorough counseling by a qualified clinician is mandatory in these cases. While standard COS (employing injectable gonadotropins) is a reasonable choice, providers may wish to offer treatment incorporating co-administration of aromatase inhibitors to minimize circulating estrogen levels (71). It is not known if ovarian stimulation itself or the use of alternative protocols affects the risk of recurrent breast cancer. 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 (72). Ideally, BSO is performed

after childbearing is completed. 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 diagnosis of BRCA mutations prior to embryo transfer. Genetic counseling is recommended for all of 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 in vitro maturation 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.

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 (55, 56, 73). While patients with lymphoma are better candidates for fertility-preservation techniques, initial therapies do not have a substantial risk of gonadotoxicity and 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 already been exposed to gonadotoxic therapies (74). While these patients may be candidates for ovarian stimulation for oocyte or embryo cryopreservation (75), 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 (30).

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 adolescents who are peripubertal but still premenarchal (76). 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 sensitive to a variety of 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 is especially recommended.

Males

Ejaculated sperm cryopreservation. Sperm cryopreservation is the standard fertility-preservation method offered to most males. Semen collection by masturbation is feasible and successful in the majority of postpubertal male patients with cancer. Semen collection should be performed prior to the administration of gonadotoxic therapies such as chemotherapy or radiation therapy. Ideally, two to three ejaculated samples should be obtained to provide adequate numbers of sperm sufficient to yield several vials for cryopreservation.

Some men may be unable to ejaculate by masturbation, especially young teenagers. Counseling and a comfortable environment to collect may be helpful. 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. For these young men or for men who are unable to ejaculate, the following therapeutic options should be considered to obtain ejaculated sperm for cryopreservation:

Use of phosphodiesterase type 5 (PDE-5) inhibitors. While these 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 (77). 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. 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 (78).

Electroejaculation. The non-specific stimulation of pelvic tissues including the prostate and seminal vesicles via a

transrectal probe may lead to seminal emission (79). Electroejaculation must be conducted under anesthesia, unless the patient also has a concurrent complete spinal cord injury.

Collection, processing, and cryopreservation of retrograde ejaculate. Some men suffer from retrograde ejaculation, which may result from surgery (autonomic or pelvic nerve injury, bladder neck injury, etc.) or certain medications (alpha-antagonists). Alpha-agonists such as pseudoephedrine can be used with care in some of these men to restore antegrade ejaculation (80). For those men who are not candidates for alpha-agonists and 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 (80). Numerous protocols for this process are available. They generally include medical urinary alkalinization and 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 or have no viable sperm or severe oligozoospermia in the ejaculate. Sperm may be obtained via multiple techniques including percutaneous epididymal sperm aspiration (PESA), testicular sperm extraction (TESE), testicular sperm aspiration (TESA), and microsurgical epididymal sperm aspiration (MESA).

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 (81, 82). 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 pursuing fertility preservation may be found to have azoospermia or other severely abnormal semen analysis findings such as necrozoospermia (dead sperm), severe oligozoospermia, or cryptozoospermia (rare sperm found only in the centrifuged, pelleted semen sample). These markedly abnormal semen analysis results may jeopardize fertility preservation. If possible, repeat semen testing with possible cryopreservation should be performed to reassess the semen and confirm these findings. While some men with severe oligozoospermia may successfully preserve their fertility through cryopreservation of sperm from one or more ejaculations, other men with severely impaired semen parameters may be candidates for procedures to surgically extract sperm for cryopreservation, even in men with testis cancer in a solitary testis (83).

Testicular tissue extraction with cryopreservation is an effective and proven procedure used routinely for men with obstructive azoospermia and nonobstructive azoospermia (84). 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). Patients pursuing fertility preservation who suffer from azoospermia, severely impaired semen parameters jeopardizing effective fertility preservation, or persistent inability to ejaculate are potential candidates for this method of fertility preservation. 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 central venous access device placement.

Investigational

The following approaches still should be considered experimental:

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 (85). Some animal studies revealed promising results, but human studies failed to demonstrate fertility preservation or more rapid return of spermatogenesis after chemotherapy.

Cryopreservation of testicular tissue in prepubertal boys. Several investigators are studying the process of germinal epithelial stem cell isolation and cryopreservation (86, 87). The ultimate goal is transplantation of this tissue back into the patient after completion of cancer therapy, with resumption of spermatogenesis. To date this procedure is purely investigational and has not demonstrated efficacy in humans. Some centers are offering investigational cryopreservation of testicular tissue from patients who have not yet reached spermarche, as a potential means of fertility preservation in these individuals who have no mature sperm available for cryopreservation.

Several studies in animal models have demonstrated the efficacy of germinal epithelial transplantation xenografted into immunosuppressed mice. These manuscripts reported spermatogenesis, pregnancies, and live births using sperm produced in this xenografted setting (88, 89). To date, no such reports with human sperm have been published, and such an approach would likely face significant regulatory hurdles.

SPECIAL CLINICAL CONSIDERATIONS

Male Patients

Testicular cancer. Men suspected of having testicular cancer can be offered sperm cryopreservation prior to orchiectomy. 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. 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 and this testicular tissue may represent the only source of viable sperm for cryopreservation in some patients (90).

Children and adolescents. Children and adolescents represent a special patient group that must be approached thoughtfully. For individuals who have undergone puberty with the initiation of sperm production, their reproductive health is as susceptible to the detrimental effects of cancer therapy as

is a fully developed adult. 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 (91). Working with these individuals and their parents requires an approach sensitive to a variety of levels of physical and psychological development. Puberty with the initiation of sperm production is often heralded by nocturnal emission, but may be present in adolescents prior to their first nocturnal emission event. Assessment of urine samples for sperm may shed further light on the presence of spermatogenesis in these patients (92).

SUMMARY

- Fertility-preservation technologies are rapidly evolving with hope that new and refined techniques will emerge.
- Patients facing treatments likely to impair reproductive function deserve prompt counseling regarding their options for fertility preservation and rapid referral to an appropriate program.
- At the present time, embryo, oocyte, and ejaculated or testicular sperm cryopreservation remain the principal established modalities for fertility preservation.
- Ovarian tissue cryopreservation, prepubertal testicular tissue cryopreservation, and the use of GnRH analogs in both females and males still should be viewed as investigational.

CONCLUSIONS

- Fertility-preservation programs should offer patients:
  - Rapid access to an interdisciplinary medical team including oncologists, reproductive endocrinologists, urologists, reproductive surgeons, mental health professionals, and geneticists.
  - An experienced ART program that offers a full complement of fertility-preservation techniques on short notice.

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