Fertility Considerations in Pediatric and Adolescent Patients Undergoing Cancer Therapy

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KEYWORDS

• Pediatric • Cancer • Survivorship • Infertility • Fertility preservation

KEY POINTS

- Survivors of pediatric cancer are at increased risk for infertility and premature hormonal failure.
- Surgeons caring for children with cancer have an important role to play in understanding this risk, as well as advocating for and performing appropriate fertility preservation procedures.
- Fertility preservation options in males and females vary by pubertal status and include nonexperimental (oocyte harvest, ovarian tissue cryopreservation, sperm cryopreservation) and experimental (testicular tissue cryopreservation) options.

BACKGROUND

A baseline risk of infertility exists in the general population. Approximately 1% of women will experience premature menopause, leading to infertility, and 1% of males will have abnormal or absent sperm counts or function.[1] However, for survivors of pediatric and adolescent cancer, this risk can be much higher owing to the effects of therapy.[2–4] This circumstance may lead to the inability to conceive a biological child and to hormonal dysfunction.

As childhood and adolescent cancer survival rates continue to increase, the number of survivors is growing. With current 5-year survival rate of more than 85%, it is estimated that there are now 500,000 survivors living in the United States, a number that is

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increasing each year.[5] This circumstance has led to an increased emphasis on managing the late effects related to the therapies used to cure these diseases. In particular, the gonadotoxic effect of radiation therapy (RT) and chemotherapy have been identified as one of the most important concerns of parents and young adult survivors of childhood cancer.[6,7]

It is therefore of critical importance to address the risk of gonadotoxicity and the potential impact of the treatment plan on future fertility with each patient and family as early as possible after diagnosis. This process enables the medical team to begin discussions with the patient and family regarding possible fertility preservation options. Surgeons caring for children with cancer have an important role to play in (1) understanding which patients are at increased risk of infertility, (2) advocating for appropriate fertility preservation services, and (3) performing fertility preservation procedures and working to coordinate these with other sedated procedures to minimize anesthesia exposures.

BASICS OF RISK ASSESSMENT

The risk of gonadotoxicity is not uniform across all patients and treatment plans; thus, patients and families must be counseled about their individual risk so they can make the most informed decision regarding their fertility preservation options. Their risk depends on their sex, age at the time of treatment exposure, and treatment specific to their cancer diagnosis.

Age and Sex

Male patients are at similar risk of gonadotoxicity regardless of age at time of therapy.[8] The risk is present beginning with the first doses of chemotherapy or RT. Sertoli cells (sperm-producing cells) in the testes are exquisitely sensitive to the gonadotoxic effects of therapy, even at a young age. Therapy-induced loss of Sertoli cells leads to temporary azoospermia, allowing for recovery over time, typically within the first 5 years after chemotherapy. However, if too many Sertoli cells are lost, as with more intense therapy, the azoospermia may be permanent.[9]

Leydig cells are responsible for testosterone production and necessary for progression through puberty. These cells are more resistant to the gonadotoxic effects of therapy.[10] Therefore, this article focuses on the effects of chemotherapy on gamete production and preservation. Because Leydig cells are much more resistant to therapy than the Sertoli cells, it is common to have a loss of sperm production (fertility) while still preserving normal testosterone levels and the ability to progress through puberty.[10]

Females are born with a defined number of primordial follicles (bank of potential eggs) and this number decreases over their lifetime. The primordial follicles have 3 potential fates:

1. Remain quiescent as the “ovarian reserve,”
2. Become activated to grow and ovulate at puberty and beyond, or
3. Become activated to grow and undergo atresia.

Over time, the ovarian reserve is gradually depleted, and at the point the primordial follicle reserve falls below a critical level (typically 1000 primordial follicles), menopause occurs.[11] Owing to the effects of chemotherapy and radiation on the ovary, the primordial follicle reserve can be depleted prematurely, resulting in premature ovarian insufficiency (POI), which is defined as women who experience menopause-like symptoms before the age of 40 years.[12] Because prepubertal patients have

significantly more primordial follicles and their ovaries have not yet begun folliculogenesis, they have a higher threshold for POI from gonadotoxic chemotherapy.[13] Patients who do not resume ovarian function within 5 years after cancer therapy are said to have acute ovarian failure.[14]

It is important to note that, although menses and oocyte function are closely related, it is possible to have menstrual cycles without follicle development and release of an oocyte. This condition is known as an anovulatory cycle and is a result of disruption in the hypothalamus–pituitary–ovarian axis. Thus, resumption of menses after therapy is not always a reliable indicator of ovarian reserve. A female childhood cancer survivor could experience POI in her teenage years, in her 20s, or in her 30s, depending on her treatment regimen.[15] Current risk assessment aims to predict who will undergo POI at the youngest ages to provide tissue preservation opportunities.

Treatment-Related Factors

Surgery

Surgery is a mainstay of cancer therapy in pediatric and young adult patients for many diagnoses. Surgery involving removal of gonadal tissue or reproductive organs may impact future fertility and the ability to have one's own biological child. Certainly, males who require bilateral orchiectomy will no longer produce sperm and will not be able to sire a pregnancy. More common is the removal of 1 testis, in which case the remaining testis will continue sperm production. Although the rate of sperm production will now be roughly 50% of prior, it is unlikely to affect fertility.[16] Males are also at risk of nerve damage during abdominal surgery, most commonly with retroperitoneal lymph node dissection.[17] These patients have impaired ejaculation, but may continue to produce normal sperm that can be extracted by testicular sperm extraction (TESE) or aspiration.

As with male patients, it is rare for the treatment of childhood and adolescent cancer in females to require bilateral oophorectomy. Should this be the case, the ability to conceive a biological child would be lost. In cases of planned bilateral oophorectomy, patients may have the option to undergo ovarian stimulation and oocyte retrieval before surgery or to have a small portion of ovarian tissue cryopreserved based on an intraoperative assessment of the surgical specimen. The removal of 1 ovary does decrease the oocyte pool for that individual, theoretically increasing the risk of POI. Because of compensatory mechanisms in the remaining ovary, to date it is unclear if removing 1 ovary decreases the remaining oocyte pool to any clinically significant degree.[18]

Radiation therapy

Male gonadal tissue is exquisitely sensitive to damage from RT.[9] Doses of more than 4 Gy to the testes are likely to result in permanent azoospermia. Even as little as 2 Gy may cause abnormalities with low sperm counts or abnormal function that are unlikely to recover.[9,19]

Ovarian tissue is also quite sensitive to RT. Prepubertal females do show some relative resistance to the effects of radiation, but permanent dysfunction can be seen with as little as 15 Gy. Postpubertal females are likely to see ovarian insufficiency with greater than 10 Gy[2,19] (**Fig. 1**).

Owing to the low dose thresholds at which permanent damage is seen, direct radiation to gonadal tissue is not necessary to experience severe dysfunction. Rather, scatter radiation alone can cause significant damage.[4] The use of proton radiation may help to limit the field of scatter radiation, but photon radiation still offers superior disease control under some circumstances and thus is still commonly used.[20]

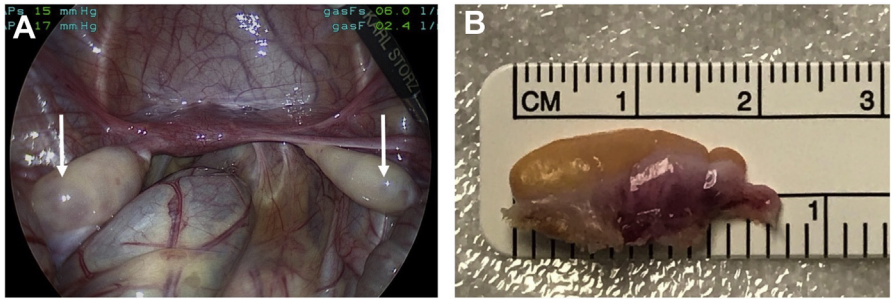

Fig. 1. (*A*) Ovarian tissue cryopreservation (OTC) in prepubertal girl. Note the follicles (*arrows*) on the ovarian cortical surface. (*B*) Size of unilateral oophorectomy specimen in 2.5-year-old girl.

Discussion with the treating radiation oncologist can help to predict the degree of scatter and potential exposure to gonadal tissues.

Chemotherapy

Multiagent chemotherapy remains the mainstay of cancer treatment for children and adolescents. Alkylating agents carry the greatest risk of gonadotoxicity and are the most widely studied.[21] The cyclophosphamide equivalent dose (CED) is discussed elsewhere in this article and was developed to help ascertain the risk of gonadotoxicity with cumulative doses of alkylating agents in pediatric and adolescent chemotherapy regimens. Guidelines recently published by the Pediatric Interest Network of the Oncofertility Consortium focus solely on this patient population. Males receiving a CED of more than 4 g/m^2 are at significant risk of permanent damage to Sertoli cells resulting in abnormal or absent sperm count. Doses of cisplatin of more than 500 mg/m^2 place males at risk of abnormal sperm motility or number.[8,19]

In postpubertal female patients, a cumulative CED of 4 g/m^2 increases the risk of POI significantly, and 8 g/m^2 will categorize a similar patient as at high risk of POI. As with RT, prepubertal females are relatively protected from gonadotoxic effects, with cumulative doses of 8 g/m^2 placing survivors at significant risk and more than 12 g/m^2 necessary to be categorized as being at high risk of POI.[12,19]

There is some preliminary evidence that anthracycline chemotherapy may increase the risk of gonadotoxicity, particularly in mouse models, but more investigation is needed before factoring this point into the patient risk assessment.[22] Likewise, newer classes of anticancer medications such as antibody therapy, immune-modulating agents, and targeted drug therapy are playing an increased role in the treatment of childhood and adolescent cancers, and their effects on fertility are not yet clear.

The effects of chemotherapy regimens (as in multiple treatment regimens with relapsed disease) and RT are additive when determining the risk of gonadotoxicity for any patient.[23,24] Patients undergoing stem cell transplantation are at high risk for gonadotoxicity and future infertility.[19] Many conditioning regimens contain high doses of alkylating agents with or without total body irradiation, particularly those for myeloablative conditioning. Patients receiving a reduced intensity conditioning regimen may have a less intense conditioning regimen and particular attention will need to be paid to the medications and dosages in use to assess the risk properly.

Risk Calculation Tools

Calculating the risk of gonadotoxicity and potential infertility from any cancer treatment is an evolving science. As the number of childhood and adolescent cancer

survivors grows, so does the information regarding their outcomes and toxicities from prior therapy. In addition, as this population ages, the effect on biological reproduction becomes more apparent. There are several tools available to clinicians to aid in providing the most up-to-date information in counseling patients at the start of therapy and continuing into survivorship.

1. Cyclophosphamide equivalent dosing: The cumulative dosing of cyclophosphamide and its relationship to gonadotoxicity has been well-established.[24] It is also established that alkylating agents, as a class of chemotherapy drugs, are gonadotoxic. However, dosing regimens for various alkylating agents are not interchangeable. Thus, Green and colleagues[24] developed the CED equation to standardize dosing regimens and allow universal risk stratification. Calculations can be done by hand using cumulative doses of various agents, or completed via an online calculator (https://fertilitypreservationpittsburgh.org/fertility-resources/fertility-risk-calculator/).
2. The Pediatric Interest Network of the Oncofertility Consortium recently published updated risk tables specific to the pediatric and adolescent population.[19] These tables are specific to males and females and include radiation exposure.
3. There is an online calculator available to help determine the risk of acute ovarian failure published by Clark and colleagues.[14] This tool helps to predict which female patients will not recover ovarian function after therapy, as with high-dose alkylating agent chemotherapy or RT.
4. The International Guideline Harmonization Group has published evidence-based guidelines on who is at risk of gonadotoxicity, who should receive fertility preservation counseling, and how to monitor survivors to aid practitioners and provide consistency in counseling this population.[21]

FERTILITY PRESERVATION OPTIONS STRATIFIED BY TREATMENT TIMING, PUBERTAL STATUS, AND SEX

The age and pubertal status of the pediatric patient are critical when considering fertility preservation options. The American Society for Reproductive Medicine (ASRM) released a committee statement in December 2019, which states that "ovarian tissue banking is an acceptable fertility-preservation technique and is no longer considered experimental."[25] This statement includes pediatric ovarian tissue cryopreservation (OTC), although leaders in pediatric fertility preservation continue to recommend treating prepubertal patients on investigational protocols.[26,27] Organizing females and males based on age and pubertal status is a useful way to begin to examine the fertility preservation options (**Table 1**). Whenever possible, removal of ovarian tissue before the start of therapy ensures the healthiest and most numerous pool of primordial follicles.[15] For males undergoing testicular tissue cryopreservation or postpubertal males, surgical tissue removal before the start of therapy results in the highest quality tissue for preservation, but tissue can have identifiable germ cells after chemotherapy, with a CED of more than 7 g/m^2 representing the accepted cut-off point for sterility.[28] For both OTC and testicular tissue cryopreservation (TTC), chemotherapy may begin within 24 hours and RT in 5 to 7 days after surgery.

Prepubertal Males

Until the onset of puberty, males do not produce mature sperm. The only pretreatment option for males at significant risk of infertility is to undergo unilateral testicular biopsy for TTC. This option is experimental and has not produced any human live births to

Table 1
Gonadal tissue preservation options based on timing of treatment, sex, and pubertal status

		Before Treatment	During Treatment	After Treatment
Males[a]	Prepubertal	TTC	TTC	N/A
	Peripubertal	Sperm baking TESE TTC	TTC	N/A
	Postpubertal	Sperm banking TESE TTC[b]	TTC	TESE
Females[a]	Prepubertal	OTC	OTC	Oocyte harvest OTC
	Postpubertal	Oocyte harvest OTC	OTC	Oocyte harvest OTC

Abbreviations: N/A, not applicable; OTC, ovarian tissue cryopreservation; TTC, testicular tissue cryopreservation.
[a] Natal designation.
[b] If inadequate sperm specimen.

date. However, the recent report of a live birth from transplanted cryopreserved testicular tissue in a primate represents very promising scientific progress.[29] The testicle biopsy provides a source of spermatogonial stem cells for future maturation and reimplantation.[28,29] Typically, 0.5 cm^3 of tissue is sufficient for cryopreservation and results in an acceptable cosmetic outcome, size, and growth of the remainder of the testicle (**Fig. 2**). The procedure has a very low complication risk and is most often combined with other necessary surgery or procedures requiring general anesthesia.[30]

Postpubertal Males

Sperm banking is always the first-choice option for fertility preservation in any male able to produce an adequate specimen. Compared with their female counterparts, males are much less likely to experience hormonal failure as a result of their therapy, so preserving sperm is satisfactory for future fertility. Unlike other fertility preservation options that can be performed in patients who have already received limited doses of chemotherapy, including alkylating agents, it is essential that sperm banking be performed before any therapy owing to the risk of DNA damage to any mature sperm that

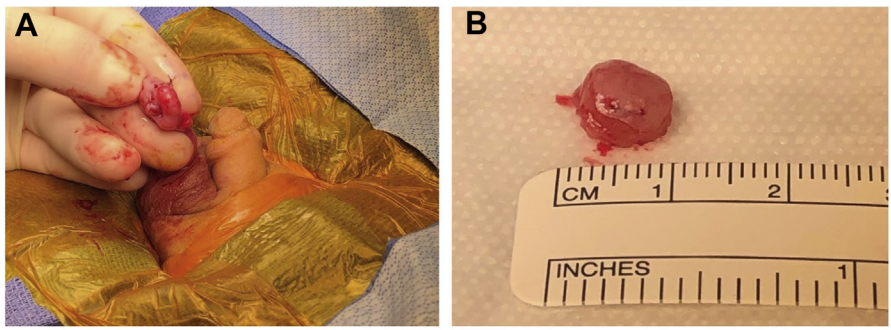

Fig. 2. (*A*) Testicular tissue cryopreservation (TTC) in 3-year-old boy. (*B*) Size of testis biopsy specimen in 3-year-old boy.

would be collected.[31] Predicting which patients will be able to produce an adequate specimen is challenging, but this option can be offered to any male who has reached Tanner 3 stage of development or has begun having nocturnal emissions. The next potential barrier is determining the child's familiarity with and comfort with masturbation. Streamlining this discussion through a dedicated fertility preservation clinician (nurse, advanced practice provider, or physician) with a fixed routine for this conversation can help to alleviate any patient discomfort about engaging in this discussion. For patients who are not able to produce a sperm sample, TTC for cryopreservation of testicular tissue and TESE for extraction and freezing of mature sperm are options.

Prepubertal Females

Until the onset of menarche, a female is considered prepubertal, and ovarian stimulation for oocyte cryopreservation (egg freezing) is not an option for fertility preservation. For these patients, the only pretreatment fertility preservation option is OTC, typically under a combined anesthesia for another needed medical procedure and involving unilateral oophorectomy by laparoscopic approach.[32] A patient can typically recover from the surgery and begin chemotherapy within 24 hours and begin RT within 5 to 7 days. If the therapy needs to begin imminently and time does not allow for surgery before beginning therapy, then the OTC may be scheduled after 1 or 2 rounds of therapy, possibly in combination with interim procedures that may require general anesthesia and before the patient approaches gonadotoxic doses of therapy.

For girls who are unable to harvest oocytes before chemotherapy initiation, including those who undergo OTC, there may be an option for harvesting oocytes in the late teen or early adult years when their remaining ovarian reserve is at its maximum. Although this post-therapy fertility preservation option should not preclude appropriate upfront fertility preservation counseling, it can be considered as an adult for survivors of pediatric cancer who want to maximize their options for future pregnancy.

Postpubertal Females

For a teenage or young adult patient who has achieved menarche, ovarian stimulation for mature oocyte cryopreservation (egg freezing) is recommended if possible, and the ASRM advocates this method as the most reliable way to preserve fertility.[25] However, many postpubertal females cannot delay the start of therapy for the approximately 2 weeks needed for hormone stimulation before egg retrieval. In addition, this fertility preservation option preserves fertility, but does not provide an option for the restoration of hormone function in the future. For some patients, both egg freezing and OTC are options and can be done in sequence, which provides the maximum range of fertility preservation options. Thorough fertility preservation counseling for postpubertal patients and families should include a discussion of these options and the opportunity to do both if time and patient circumstances allow, especially now that OTC is no longer considered experimental by ASRM. Counseling should include an explanation of the need for a transvaginal ultrasound examination and needle retrieval for egg freezing, because these procedures may be challenging for some teenagers. For patients who undergo OTC, the procedure can be combined with other necessary surgery or procedures under 1 anesthetic exposure. The Fertility and Hormone Preservation and Restoration team at Lurie Children's in Chicago advocates laparoscopic unilateral oophorectomy to provide high-quality ovarian tissue for long-term storage and for the most reliable hemostasis, with a minimal impact on the patient's own innate ovarian function as the remaining ovary compensates.[18,33,34]

UNIQUE CONSIDERATIONS IN PEDIATRIC FERTILITY PRESERVATION

Success of Sperm Banking in Adolescent Males

Sperm banking is the preferred approach for fertility preservation in any male patient who is able to provide an ejaculated semen specimen before the initiation of chemotherapy. This process must take into account both the physical and emotional maturity of the patient, as well as the religious and cultural views of the family. However, with the proper fertility counseling resources, the chances of successful sperm cryopreservation can be maximized. Providers often underestimate the chance of successful sperm cryopreservation, and these biases or preconceptions should not interfere with offering and encouraging this option.

Sperm banking continues to be underused in adolescent male patients. A Canadian study found that fewer than 25% of eligible male adolescents attempt to bank sperm.[35] In a survey of pediatric oncology providers, only 46% reported they refer male pubertal patients with cancer to a fertility specialist before cancer treatment more than 50% of the time.[36] More encouragingly, in a French multicenter study, it was noted that referrals for sperm banking increased 9.5% annually from 1973 to 2007.[37] Additionally, the percentage of younger patients with cancer who cryopreserved sperm increased, particularly in the 11- to 14-year-old age group, where it increased from 1% in 1986 to 9% in 2006. With a continued emphasis on the importance of fertility preservation counseling and services, this use will hopefully continue to increase.

Efforts to increase the use of sperm cryopreservation techniques require providers to better understand the factors predictive of successful banking attempts. The age range of pubertal development varies widely, and patients who have begun having nocturnal emissions or reached Tanner stage 3 should be offered this option, even if they are at a younger chronologic age. In a multi-institutional study of 146 male patients surveyed at the start of chemotherapy, meeting with a fertility specialist (odds ratio [OR], 3.44), parent (OR, 3.02) or provider (OR, 2.67) recommendation to bank, and greater adolescent self-efficacy to bank (OR, 1.16) were associated with successful sperm banking.[38] They also found that banking was successful in 23% of Tanner stage 3, 31% of Tanner stage4, and 52% of Tanner stage 5 patients. It was also successful in 40% of patients who denied a history of nocturnal emission and 15% of patients who denied a history of masturbation. In another study of 80 males aged 13 to 19 years, 84% were able to produce semen by masturbation and 66% had adequate quality for cryopreservation.[39] A follow-up report of 114 males from the same institution reported a 93% rate of semen production by masturbation and 68% rate of successful sperm cryopreservation.[40] Among 11 patients with a median Tanner stage of 3 who were unable to produce an ejaculated specimen by masturbation, 100% had successful cryopreservation after electroejaculation in the this study.

The Role of Hybrid Testicular Tissue Cryopreservation and Testicular Sperm Extraction in Peripubertal Males Unable to Sperm Bank or Those Who Produce an Inadequate Specimen

A hybrid approach to fertility preservation is often beneficial for peripubertal males. It is not uncommon for these efforts to produce an oligospermatic specimen or even be unsuccessful in their attempt at banking. The sperm is stored in aliquot vials with each vial representing 1 opportunity for future insemination. We recommend consideration of additional fertility preservation interventions to males unable to store 5 to 10 good vials of sperm. For peripubertal males who are likely to have mature sperm in the testicle but are unable to produce a semen sample, TTC can

be combined with TESE. These patients are typically Tanner stage 3 to 4, with testicular volumes large enough to allow taking a 1.0 × 0.5-cm wedge for TTC plus a similar size wedge for sperm extraction through the same incision. This hybrid approach ensures that all future restoration options using spermatogonial stem cells remain available to the patient, while also maximizing the opportunity to store mature sperm for in vitro fertilization.

The Role of Gonadotropin-Releasing Hormone Agonists in Female Fertility Preservation

The role of ovarian suppression with gonadotropin-releasing hormone agonists during chemotherapy to help preserve fertility and prevent ovarian failure remains controversial.[41] A meta-analysis of adults with early stage breast cancer demonstrated that patients who received gonadotropin-releasing hormone agonist therapy had their risk of POI decreased by one-half ($P<.001$).[42] However, in a randomized trial of young patients with lymphoma after 5 years of clinical follow-up, there was no difference in the rate of primary ovarian failure or pregnancy rate in the treatment and control groups.[43] The ASRM practice guidelines indicate that gonadotropin-releasing hormone analogs may be given to select patients with breast cancer, but should not be used in place of other fertility preservation measures.[25]

The Usefulness of Ovarian Transposition

Ovarian transposition is a consideration for girls receiving radiation to the pelvis. Transposition can be permanent or temporary. The standard approach for girls undergoing pelvic radiation involves transposition of the ovary to the paracolic gutters with the division of the ligamentous attachments.[44] The effect of dividing these attachments and relocating the tube and ovary out of the pelvis on future fertility is poorly understood. In some cases, relocation back to the pelvis after therapy completion is performed. Alternatively, temporary transposition for the short duration of treatment for girls receiving brachytherapy can be achieved without division of the ligamentous attachments using a laparoscopic approach.[45] A transcutaneous suture is used to fixate the ovary to the abdominal wall as far out of the pelvis as possible and the suture is cut after completion of therapy to allow the ovary to fall back into the pelvis.

Ovarian transposition has been reported in at least 37 patients from 6 studies in patients under the age of 20.[46] One study reported 4 associated complications, including small bowel obstruction, dyspareunia, and pelvic adhesions causing tubal obstruction.[47] Despite the sound logic behind moving the ovary out of the radiation field, the benefit of transposition for decreasing the risk of ovarian failure or infertility is unproven. In fact, in patients who received pelvic RT for Hodgkin's lymphoma, ovarian transposition did not seem to modify the risk of ovarian insufficiency.[48]

FUTURE DIRECTIONS IN PEDIATRIC OVARIAN TISSUE CRYOPRESERVATION

Optimal Surgical Approach for Pediatric Ovarian Tissue Cryopreservation

For female patients undergoing OTC, debate exists over the optimal extent of the ovarian harvest procedure. A recent systematic review found that 57% of patients underwent total oophorectomy and 43% had partial oophorectomy.[46] Advocates for unilateral oophorectomy cite (1) a potential improved safety profile, (2) the maximization of the amount of cortical tissue for cryopreservation and future reimplantation, and (3) evidence that unilateral oophorectomy is not associated with reduced fertility or premature menopause.[32] The cut surface on the ovary for partial oophorectomy is a potential source of hemorrhagic complications, which are avoided with unilateral

oophorectomy. The few reported cases of postoperative bleeding requiring transfusion or re-exploration occurred in patients who had undergone partial oophorectomy.[46] Furthermore, when cortical strips are reimplanted, the duration of fertility restoration is limited. Preserving multiple cortical strips from the entire ovary allows for multiple attempts at reimplantation, as well as repeat reimplantation if the hormonal restoration effect abates. The rate of pregnancy after reimplantation is 29% and live birth rate is 23% based on the most reliable data from 5 major centers published in a 2017 review.[49] In a review of 210 women who underwent ovarian transplantation, 170 of which were from their own frozen ovarian tissue, more than 78% achieved restoration of ovarian function.[50] However, the duration of the restored ovarian function was quite variable, ranging from less than 1 year to more than 5 years. In a systematic review of worldwide data on transplantation of thawed ovarian tissue, 360 ovarian transplant procedures were performed in 318 women. In this review, endocrine function was restored in 95% of those for whom data were available, and 131 pregnancies were achieved in 95 patients, with a total of 93 children born to 69 women. This review also noted that the youngest reported patient to undergo OTC with tissue use was 9 years of age, and that younger patients (average, 26.4 years; range, 9–38 years) who underwent OTC were more likely to succeed in having a live birth than older patients.[51]

With regard to the effect of unilateral oophorectomy on ovarian reserve, a systematic review and meta-analysis compared the success of assisted reproduction in women who had undergone unilateral oophorectomy with those with 2 ovaries. It found a comparable overall weighted odds of clinical pregnancy, although those who had undergone oophorectomy demonstrated evidence of decreased ovarian reserve.[52] In a population-based study from Norway, women who had undergone unilateral oophorectomy progressed through menopause only 1 year earlier than those with both ovaries.[18]

Proponents of partial oophorectomy cite the principle of “first do no harm” and emphasize the importance of preserving a maximal amount of native ovarian reserve. There are no data to suggest that women with ovarian tissue exposed to gonadotoxic chemotherapy have a higher chance of spontaneous pregnancy after partial compared with total oophorectomy. Further work is required to determine the optimal surgical approach, which may vary based on the exact treatment regimen. For females whose treatment includes very high CEDs and significant pelvic radiation, which places them at extremely high risk of infertility and premature ovarian failure, unilateral oophorectomy maximizes the options for fertility and hormone restoration while minimizing surgical risks. However, for those females whose treatment places them at a more modest risk of infertility, there may be an advantage to preserving as much native ovarian function as possible. This goal must be balanced against increasing evidence of successful restoration of endocrine and fertility function from OTC. The long-term effects on fertility and hormone restoration are required to determine if the theoretic benefits of partial oophorectomy outweigh the potential increased surgical complication rate and decreased volume of stored tissue compared with unilateral oophorectomy.

Optimal Processing Technique for Prepubertal Ovarian Tissue Cryopreservation

The protocols for processing pediatric ovarian tissue for OTC use the same technique established for adult patients.[53] The process involves thinning the ovarian tissue while removing the medullary region, where growing follicles are located, while preserving the cortical region, where the primordial follicles exist in dense stroma. The thinning process allows cryoprotectant to penetrate the tissue, which is then cut into cortical strips

that are stored in individual vials so that they may be thawed individually in the future. The prepubertal ovary is fundamentally different from the postpubertal ovary because it is much smaller, typically 1 to 2 cm^2, and lacks a clear cortical–medullary junction.[53] In postpubertal patients, the tissue processing involves thinning the cortex with a tissue slicer, and then cutting the tissue into cortical strips that are stored in individual vials so that they may be thawed individually in the future. Our experience with processing ovarian tissue from prepubertal patients has revealed that primordial follicles exist within the tissue fragments of OTC processing media, which does not occur in media processed from adult patients and is thought to only contain the medullary regions (**Fig. 3**). More research is required to optimize the technique for processing in an effort to preserve the most primordial follicles that could restore both fertility and hormones in these pediatric patients once transplanted. Although the main objective in OTC is to preserve the ovarian cortex, which contains the majority of primordial follicles or ovarian reserve, during the tissue processing, small antral follicles in the medulla are disrupted and cumulus oocyte complexes are released into the media.[54,55] In a process referred to as ex vivo in vitro maturation, these cumulus oocyte complexes can be recovered and matured in vitro to obtain eggs arrested at metaphase of meiosis II, which may be possible to cryopreserve for future use.[27]

SUMMARY AND FUTURE DIRECTIONS

Advances in clinical pediatric oncology care leading to dramatically improved survival now present challenges of long-term quality-of-life issues in survivorship, including fertility and hormone function. Multicenter data will be essential to refine the risk assessment for future pediatric patients based on the outcomes of adult patients who had gonadal tissue preservation before gonadotoxic therapy compared with those who did not. Further research into fertility and hormone restoration options and outcomes is necessary for adult survivors of childhood cancer who underwent gonadal tissue preservation. Surgeons caring for pediatric patients with cancer can remain knowledgeable advocates in fertility preservation, incorporate fertility preservation options pretreatment or early in treatment, and perform procedures to preserve pediatric ovarian and testicular tissue when safe and necessary for those children at most significant risk of infertility.

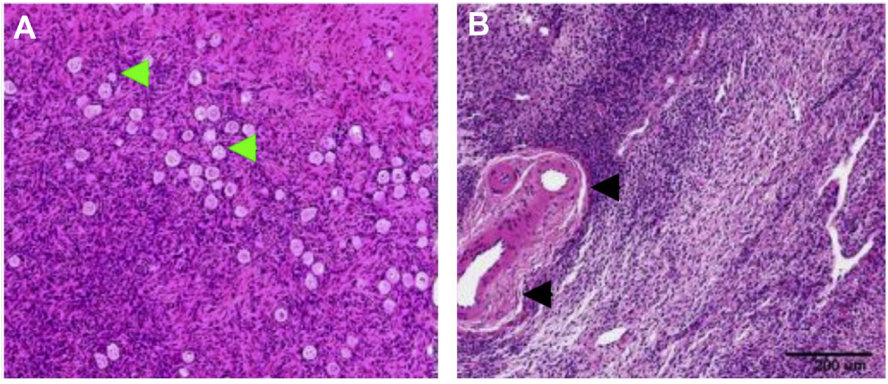

Fig. 3. Tissue fragments collected from OTC processing media. (*A*) A 7-year-old girl with no previous treatment, containing primordial follicles (*green arrow*) and (*B*) a 21-year-old woman with no previous treatment, containing stroma and vessels (*black arrow*) (indicating medullary tissue without ovarian reserve).

CLINICS CARE POINTS

- Fertility preservation options exist for both prepubertal and postpubertal males and females.
- A fertility consultation should be offered to the families of all children receiving therapies that place them at increased risk for infertility or premature hormonal failure, and standardized risk assessment tools exist to help quantify this risk.
- There are both nonexperimental (oocyte harvest, OTC, sperm cryopreservation) and experimental (testicular tissue cryopreservation) options for fertility preservation, depending on the patient's sex and pubertal status.

DISCLOSURE

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