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REVIEW

Oncofertility care for children, adolescents, and young adults at risk for treatment-related fertility loss

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Abstract

As therapy for childhood malignancies becomes more sophisticated and survival has improved, long-term therapy-related sequelae have emerged. Loss of reproductive potential among childhood cancer survivors is one such concern that has become increasingly recognized among patients, families, and healthcare providers. The risk status for infertility based upon therapy received, state of current reproductive technology and outcomes, and an emphasis on adequate referral and counseling for fertility preservation options are reviewed. Contributing factors to infertility are discussed, and options for female and male preservation based upon age and pubertal status are summarized. This article highlights the current state of fertility opportunities for children and adolescents undergoing therapy for cancer. Providers caring for these young patients should be familiar with such options and should routinely initiate evaluations for eligibility of fertility preservation.

KEYWORDS
oncofertility, ovarian cryopreservation, testicular biopsy

1 | INTRODUCTION

Children, adolescents, and young adults in high-income countries with malignancies have achieved a survival rate nearing 80% in recent population-level evaluations.[1–3] In concert with the rise in overall survival rate, however, it is now well known that comorbidities following cancer treatment are an increasing burden on survivors and their families, and in fact convey a lower quality of life than that experienced by age-adjusted peers who are not cancer survivors.[4–6]

High in priority for survivors of childhood cancers among the post-treatment morbidities is the loss of reproductive hormonal production and fertility experienced by many patients as a result of gonadotoxic treatment regimens at sensitive stages of life.[7,8] Along with that concern, recent work has identified several barriers to communication of infertility risks and outcomes, misunderstanding by both patients and providers of these risks, delays in or lack of referral for fertility counseling, and distress later in life when patients are faced with reproductive morbidity and have few options for conceiving

Abbreviations: ART, assisted reproductive technology; ASCO, American Society of Clinical Oncology; ASRM, American Society for Reproductive Medicine; CED, cyclophosphamide equivalent dose; COG, Children's Oncology Group; HPA, hypothalamic–pituitary axis; HSCT, hematopoietic stem cell transplant; IGHG, International Guideline Harmonization Group; OTC, ovarian tissue cryopreservation; OTT, ovarian tissue transplantation.

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Intervention	Site	Pubertal Status	Risk Level		
			Minimally Increased Risk	Significantly Increased Risk	High Level of Increased Risk
Alkylators (CED* gm/m^2)		Prepubertal	CED < 8	CED 8 - 12	CED > 12
		Postpubertal	CED < 4	CED 4 - 8	CED > 8
Heavy metal			Cisplatin		
			Carboplatin		
Hematopoietic stem cell transplant					Alkylator +/- Total body irradiation; Myeloablative and Reduced Intensity Regimens
Radiation exposure	Ovary	Prepubertal		< 15 Gy	≥ 15 Gy
		Postpubertal		< 10 Gy	≥ 10 Gy
	Hypothalamus		22 - 29.9 Gy	30 - 39.9 Gy	> 40 Gy

FIGURE 1 The Pediatric Initiative Network Risk Stratification System for gonadal failure or infertility in *female* survivors of pediatric, adolescent, and young adult cancer as determined above the level for the general population. Adapted from Meacham et al., Journal of Adolescent and Young Adult Oncology, 2020. CED, cyclophosphamide equivalent dose.

biological children.[9–12] Therefore, several leading consortia including the Children's Oncology Group (COG),[13,14] PanLIFE Consortium and International Guideline Harmonization Group (IGHG),[15–17] National Comprehensive Cancer Network,[18] American Society for Reproductive Medicine (ASRM),[19] and American Society of Clinical Oncology (ASCO)[20] among others have published statements and practice guidelines establishing the standard of care for fertility preservation and monitoring at all stages of the treatment process for children, adolescents, and young adults with cancer. In this review, we seek to bring this information to a broad pediatric oncology audience.

2 | MEDICAL ASPECTS AND CONTRIBUTORY FACTORS TO ONCOFERTILITY ISSUES

Medical treatment of many pediatric cancers, including high-risk leukemia, brain tumors, and most solid tumors in childhood carry a significant risk for direct and indirect effects on future fertility.[21,22] For females, this risk manifests as both loss of reproductive hormonal function, referred to as premature ovarian insufficiency, as well as loss of ability to conceive and carry a pregnancy to live birth, more commonly referred to as infertility.[22,23] This effect is largely due to three mechanisms of damage to the ovarian tissue: (i) direct toxicity to the granulosa cells of ovarian follicles, leading to reduction in estrogen production and follicular loss; (ii) reactionary premature recruitment of primordial follicles, leading to acceleration of follicular loss over time and reduction in ovarian reserve; and (iii) direct vascular damage due to chemotherapy and radiotherapy reducing viability of ovarian tissue.[24] For males, the effect tends to be sparing of hormonal production, leading primarily to oligozoospermia or azoospermia as a result of the variable tolerability of gamete-producing spermatogonia and stem cells to chemotherapy and radiotherapy effects.[25]

The age of onset of risk is also different between the sexes. Male patients of all ages have some level of spermatogonial cell division ongoing, and therefore those cells are at risk even at early ages.[26] In the contrary, in females, the arrested meiosis of the egg cells in the prepubertal follicle and the lack of follicular maturation prior to puberty lead to a relative protective effect.[27] Therefore, in males of all ages, a lower exposure to chemotherapy or radiotherapy treatments results in higher levels of impact on fertility, whereas younger females are relatively protected, and overall require higher doses of offending agents to experience the same detrimental effects.

It is critical to remember that the negative effects of chemotherapy and radiotherapy on fertility outcomes, especially in male patients, may begin after a single treatment or cycle of offending chemotherapy. Therefore, discussions of fertility risk and referral for evaluation for eligibility of fertility preservation strategies must be performed prior to initiation of treatment in all possible cases.[15,16] Even in situations where therapy is urgent and should be initiated immediately, implications should be discussed with the family, and the option to pursue urgent tissue preservation or sperm donation should be offered.[17,19] Special care should be taken to consider procedures such as ovarian or testicular tissue harvest, oophoropexy, or testicular transposition under the same anesthetic as primary tumor resection or establishment of central venous access for treatment.[28–30]

2.1 | Alkylating and alkylating-like medications

The primary medical agents known to cause subsequent reduction in fertility are the alkylating chemotherapies. These include cyclophosphamide, ifosfamide, procarbazine, chlorambucil, carmustine (BCNU), lomustine (CCNU), melphalan, thio-TEPA, nitrogen mustard, and busulfan.[21,23] Green et al. in 2014 described a unifying system to allow direct comparison of the gonadotoxal effects of these medications with the development of the cyclophosphamide equivalent dose (CED), which is now the standard nomenclature used to describe and predict effects on fertility of many but not all various chemotherapeutic regimens and agents.[31] Risk levels are generally described as minimally increased, significant level of risk, and high level of significant risk, and are calculated separately for pre-pubertal and post-pubertal males and females (Figures 1 and 2).[27] A CED of less than 4000 mg/m^2 in post-pubertal female patients and less than 8000 mg/m^2 in

Intervention	Site	Risk Level		
		Minimally Increased Risk	Significantly Increased Risk	High Level of Increased Risk
Alkylators (CED* gm/m^2)		CED < 4		CED ≥ 4
Heavy metal		Cisplatin	Cisplatin > 500 mg/m^2	
		Carboplatin		
Hematopoietic stem cell transplant				Alkylator +/- Total body irradiation; Myeloablative and Reduced Intensity Regimens
Radiation exposure	Testicular	0.2 - 0.6 Gy	0.7 - 3.9 Gy	≥ 4 Gy
	Hypothalamus	22 - 29.9 Gy	30 - 39.9 Gy	> 40 Gy
Surgery			RPLND	

FIGURE 2 The Pediatric Initiative Network Risk Stratification System for gonadal failure or infertility in *male* survivors of pediatric, adolescent, and young adult cancer as determined above the level for the general population. Adapted from Meacham et al., Journal of Adolescent and Young Adult Oncology, 2020. CED, cyclophosphamide equivalent dose; RPLND, retroperitoneal lymph node dissection.

pre-pubertal female patients is considered minimally increased risk, while a CED between 4000–8000 and 8000–12,000 mg/m^2 is considered significantly increased risk and a CED 8000 and 12,000 mg/m^2, is considered high level of increaesd risk for post- and pre-pubertal females, respectively.[27] In male patients, a CED less than 4000 mg/m^2 is considered minimally increased risk, while a CED greater than 4000 mg/m^2 is considered high level of increased risk.[27,32] Given the relative susceptibility of male spermatogonia to deleterious effects, the inclusion of cisplatin or carboplatin, both alkylating-like drugs, into a chemotherapy regimen is also considered minimally increased risk, while doses of cisplatin greater than 500 mg/m^2 are considered significantly increased risk for male patients.[27]

2.2 | Radiotherapy

The effects of radiotherapy on fertility can be due to either direct radiotherapy to the gonadal organ or scatter effects. Additionally, the effect of central hypogonadism due to cranial radiotherapy affecting the hypothalamic–pituitary axis (HPA) is well-recognized. The sterilizing dose of direct radiation to the gonads is higher in females than in males and decreases over time. For situations in which direct radiotherapy to the gonads is not necessary but pelvic irradiation is, such as in pelvic Ewing sarcoma or rhabdomyosarcoma, the resultant scatter effect must also be considered, and efforts should be made to remove the at-risk gonads from the area of scatter resulting in a moderate recommendation for oophoropexy or testicular transposition by the IGHG.[15,16,33] However, transposition should not be considered a sufficient approach to protect desired fertility outcomes on its own, and other modalities (gamete or reproductive tissue preservation, as indicated) should also be offered.

Direct toxicity to the HPA axis may occur at doses of 30 Gy after cranial radiotherapy for brain tumors, achieving high risk of infertility at doses of 40 Gy and higher.[27]

Males are considered to be at high risk of infertility due to radiotherapy at a direct dose to the testicles of 4 Gy. There is no protective effect in prepubertal ages due to ongoing spermatogenesis.[21,27] Females are considered to be at high risk at a dose of 15 Gy for prepubertal ages and 10 Gy for post-pubertal ages.[22,27]

2.3 | Hematopoietic stem cell conditioning regimens

The total body irradiation as well as the conditioning chemotherapeutic regimen prior to hematopoietic stem cell transplant (HSCT) are both highly toxic as well as synergistic. Both males and females are considered at high risk for infertility with HSCT conditioning, including with reduced-intensity regimens.[34,35]

2.4 | Novel therapies

It is important to recognize that in the era of targeted therapies and emerging immunotherapies (adoptive cell therapy, immune checkpoint inhibition, monoclonal antibody treatments), there is a lack of data on future fertility compromise after treatment with these regimens. IGHG guidelines are currently under revision to consider guidance for patients undergoing these therapies.

2.5 | Reproductive organ loss

Direct ovarian or testicular loss can be observed in the case of germ cell tumors, rhabdomyosarcoma, and other solid tumors, and in the context of genetic predisposition syndromes such as DICER1, Down syndrome, hereditary nonpolyposis colorectal cancer (Lynch syndrome, HNPCC), and others.[36] Loss of gonadal tissue as a result of oophorectomy or orchiectomy or detrimental effects, such as retrograde ejaculation resulting from ancillary procedures such as retroperitoneal lymph node dissection,[37] can contribute to alteration or reduction in fertility and hormone production independently of gonadotoxic chemotherapy or radiotherapy.

The most ameliorating effort that can be made to reduce the risk of hormonal insufficiency or gamete loss due to direct tumor involvement is to understand when ovarian- or testicular-sparing treatment is appropriate, and to pursue that course when feasible. For females, laparoscopic ovarian-sparing resection of masses should be attempted when preoperative hormonal workup and imaging characteristics suggest benign etiology, even in the setting of torsion and significant ovarian thinning or stretching.[38] If final pathology indicates an unexpected malignancy, subsequent ipsilateral oophorectomy should be performed. Techniques for avoiding spill of large cystic lesions should be employed to facilitate ovarian-sparing approaches in cases of large but benign-appearing cystic lesions of the ovary meeting the above criteria.

For prepubertal males, enucleation of lesions of the testicle may be performed rather than orchiectomy when tumor markers are negative, imaging is consistent with teratoma, and there is no evidence of retroperitoneal lymph node involvement. In situations felt to be equivocal, frozen section can be performed intraoperatively, reserving the ability to proceed to formal orchiectomy if needed. However, oncologic principles should be maintained, and tumor capsule and scrotum should not be violated during resection.[39,40] Any patient in which a formal orchiectomy with high ligation of cord structures has not been performed at the time of initial tumor resection, but final pathology reveals malignancy, should undergo subsequent completion orchiectomy with high ligation of cord structures as a second procedure.

When discussing ovarian tissue harvest with families, it is important to consider the effect of ovarian tissue loss followed by gonadotoxic chemotherapy in a prepubertal female. While the contralateral ovary will upregulate hormonal production, this does not adequately address the remaining ovary's adaptability when it is subsequently subjected to gonadotoxic chemotherapy. A report that included 706 women who were childhood cancer survivors, 32% of whom had reached the age of 40 years, demonstrated the occurrence of menopause 7 years earlier in females with a single ovary.[41] Furthermore, this study identified exposure to alkylating agents, increasing doses of radiation, cyclophosphamide, and procarbazine, and unilateral oophorectomy as risk factors for non-surgical menopause.[41] In this situation, consideration of the effect of prepubertal ovarian tissue resection on ultimate ovarian reserve should be carefully considered and discussed with the patient, as appropriate, and family prior to committing to ovarian tissue harvest.[42]

2.6 | Fertility preservation counseling and care

Fertility preservation has emerged as a crucial aspect of comprehensive care for children diagnosed with cancer, with the primary aim of enhancing the long-term quality of life for survivors. Patients and families who engage in fertility preservation discussions around the time of diagnosis often report a sense of hope beyond their cancer diagnosis, expressing a desire for future biological parenthood.[10,43–45] Conversely, individuals who did not receive fertility preservation counseling or are uncertain about their fertility status, often grapple with profound emotional distress, including anxiety, self-doubt, regret, lower self-esteem, and guilt regarding their reproductive health.[10,44,46–48] The failure to meet future parenthood goals is also linked to significant emotional distress concerning future relationships and aspirations to start a family.[44,48,49]

Society guidelines from the American Academy of Pediatrics (AAP), ASCO, COG, and ASRM emphasize the importance of fertility preservation consultations for all pediatric patients with cancer, irrespective of their risk profile. These guidelines stress the need for timely consultations following diagnosis and prior to initiation of cancer treatment.[45,50–52] However, several challenges hinder effective fertility preservation discussions, including quick decision-making at the time of a new diagnosis, the sensitive nature of the topic, provider knowledge gaps regarding oncofertility options, unclear referral strategies, and financial concerns associated with the costs of fertility preservation procedures.[10,45,48,53,54]

These challenges can be compounded by parents feeling the need to prioritize their child's treatment initiation and having an underappreciation of their child's future parenting plans.[10,49,54,55] It has been shown that as time progresses, future fertility potential becomes increasingly more important for survivors of childhood cancer.[10,55] Viewing a child's future reproductive health as "fertility in trust" emphasizes the long-term importance of fertility, advocating for decisions that support and keep future reproductive options open. In this light, fertility preservation can be seen as a means to enable possible future choices rather than as an extension of current parenting desires.[10]

An ideal fertility preservation discussion should be thorough, supportive, personalized, and initiated promptly following a new cancer diagnosis. Considerations should encompass a patient's age, pubertal status, risk of gonadal failure after treatment, potential treatment delays, cultural/religious concerns, healthcare system capabilities, and local legal regulations.[45] The involvement of a separate, dedicated fertility and reproductive health team can facilitate comprehensive discussions with patients and their families about infertility risk, available fertility preservation options, and alternatives to biological parenthood.[45,49,55]

In the sections to follow are specific discussions of female and male fertility options. It is also important that when counseling the patients and families, they are presented with options that exist outside of fertility preservation procedures, which include adoption, surrogacy, and the use of donor sperm/eggs or embryos.

3 | FEMALE FERTILITY PRESERVATION

3.1 | Fertility preservation options for females

Fertility preservation options depend upon several factors including, but not limited to, the patient's pubertal development, partner status, and timing of therapy. Fertility preservation options for post-pubertal females include ovarian transposition, embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation (OTC).

TABLE 1 Options for fertility preservation for female patients.

	Details	Pros	Cons
Ovarian transposition	Surgically moving ovaries out of planned radiation field	• Can reduce risk of premature ovarian insufficiency • Can be performed with minimal invasive or at concomitant surgical procedure	• Risk of damage to ovary • Scatter from radiation can still affect the ovarian tissue • Does not protect against gonatotoxic effects of systemic chemotherapy
Oocyte and embryo cryopreservation	Ovarian stimulation followed by ovulation trigger, then oocyte retrieval	• Standard of care for post-pubertal patients • Can be accomplished in approximately 2 weeks	• Requires transvaginal ultrasound/procedure and may require sedation/anesthesia in adolescents/young adults • Risks include bleeding and hyperstimulation syndrome[56]
Ovarian tissue cryopreservation (OTC)	Surgical removal of ovarian cortical tissue, processed and frozen for future reproductive restoration	• Minimal to no treatment delays following harvest • Most frequently performed method of fertility preservation in pediatric patients[29,57,59,60]	• Requires surgical procedure • Unilateral oophorectomy for OTC may hasten menopause[63]
Ovarian tissue transplantation (OTT)	Previously harvested ovarian cortical tissue thawed and surgically transplanted	• Potential restoration of reproductive hormone function and fertility • Numerous live births achieved in post-pubertal patients[60]	• Requires second surgical procedure for transplantation • May require repeat OTT (median graft survival 2–3 years)[58,60,67]

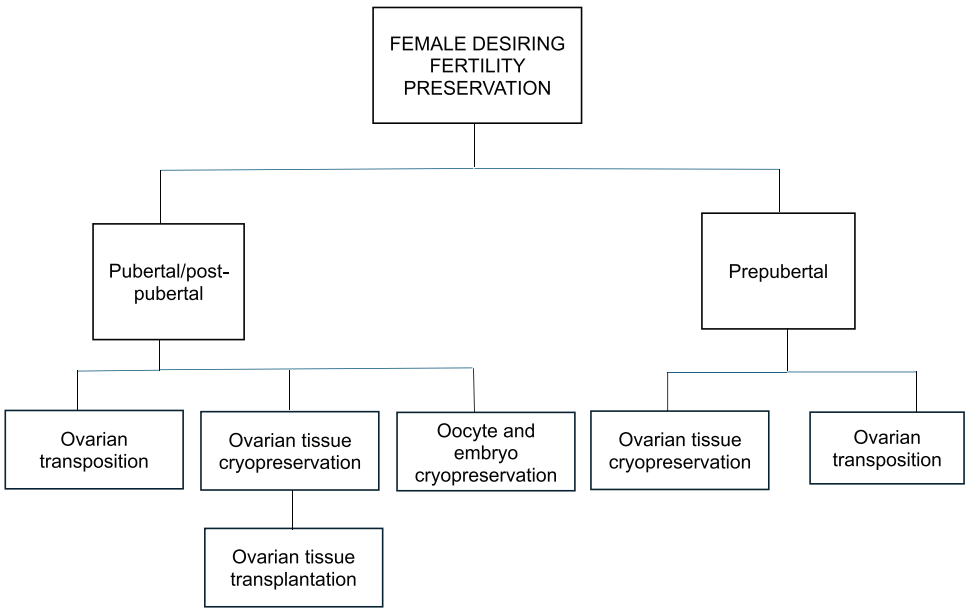


FIGURE 3 Flowchart of options for fertility preservation in female patients.

While using gonadotropin-releasing hormone (GnRH) analogs for ovarian suppression is helpful for menstrual suppression during therapy, there is insufficient evidence for their use as a fertility preservation modality. These analogs are an option for post-pubertal patients without other alternatives, and ongoing research will hopefully be able to provide data on their efficacy. Currently, ovarian transposition and OTC are the only methods available for pre-pubertal patients. Fertility preservation options are summarized in Table 1 and Figure 3.

3.1.1 | Ovarian transposition

Ovarian transposition involves surgically moving the ovaries out of the planned radiation field to minimize damage to the ovarian tissue and reduce the risk of premature ovarian insufficiency. Ideally this is performed in a minimally invasive fashion or at the time of a concomitant open surgical procedure. In addition to the standard surgical risks, ovarian transposition carries the risk of ovarian necrosis, ovarian

torsion, and pelvic pain. Ovarian transposition does not protect from the gonadotoxic effects of systemic chemotherapy.

3.1.2 | Oocyte and embryo cryopreservation

Oocyte and embryo cryopreservation have been considered standard-of-care fertility preservation options for post-pubertal patients for some time. These methods involve ovarian stimulation by gonadotropins, followed by ovulation trigger, and then oocyte retrieval. Patients with a partner or donor sperm may choose to preserve embryos rather than oocytes. With the advancement in flexible, quick start protocols, oocyte/embryo cryopreservation can be accomplished in approximately 2 weeks, making this option more readily available for patients who need to expedite the initiation of gonadotoxic therapy. Of note, traditional oocyte retrieval techniques (i.e., transvaginal ultrasound probe) may prove challenging for some adolescents, and consideration should be given to the use of transabdominal retrieval. Live birth rates from cryopreserved embryos are nearly 40%, with slightly lower birth rates for cryopreserved oocytes. Risks related to these methods include ovarian hyperstimulation syndrome and bleeding related to oocyte retrieval.[56]

3.1.3 | Ovarian tissue cryopreservation

OTC serves as a vital fertility preservation method for pediatric, adolescent, and young adult patients facing the highest risk of infertility due to gonadotoxic therapies.[27] OTC requires the surgical removal of ovarian cortical tissue to process and freeze for potential future reproductive hormone and fertility restoration. Preoperative considerations include safe timing of surgery, preoperative laboratory studies, and coordination of additional procedures. Surgery should be considered elective, and patients should be well enough from an overall clinical disease standpoint to undergo a same-day laparoscopic surgery. Some children who are critically ill at the time of a new diagnosis may benefit from initiation of systemic chemotherapy prior to proceeding with fertility preservation to ensure safe surgery and minimal residual disease.[57,58] In addition, children diagnosed with a hematologic malignancy may benefit from chemotherapy prior to OTC to allow for ovarian cortical tissue harvest while patients are in remission, as active disease can be found in ovarian tissue.[58]

Preoperative assessment includes the collection of reproductive biomarkers (anti-Mullerian hormone, luteinizing hormone, follicle-stimulating hormone, estradiol) and an infectious disease panel to comply with long-term reproductive tissue storage requirements.[29] Efforts should be made to coordinate additional procedures, such as central venous catheter insertions, bone marrow biopsy or aspiration, or lumbar puncture, with OTC to minimize repeated exposure to general anesthesia.[29] No additional imaging is required prior to OTC.

Although no consensus exists on operative techniques, laparoscopic unilateral oophorectomy is the most frequently performed surgery for ovarian cortical tissue harvest in pediatric patients,[29,57,59,60] and multiple series report that children can safely initiate chemotherapy and radiation postoperatively for their underlying disease without experiencing treatment delays.[29,61] Although laparoscopic unilateral ovarian cortical tissue harvest is a safe and relatively short operative procedure, other methods including partial oophorectomy and ovarian tissue biopsy have been associated with higher rates of postoperative bleeding complications compared to unilateral oophorectomy.[59,62] Unilateral complete oophorectomy in otherwise healthy women, however, has been shown to hasten menopause by approximately 1 year.[63] In another report, however, there was no significant difference in rates of premature ovarian failure when comparing females who underwent bone marrow transplant with or without oophorectomy for OTC.[64]

Ovarian tissue transplantation (OTT) involves utilizing thawed ovarian cortical tissue for the restoration of ovarian reproductive hormone function and fertility. Ovarian cortical tissue can be transplanted in an orthotopic position (ovary or peritoneal bursa) or a heterotopic location (subcutaneous tissue of the arm or abdomen).[58,62] Orthotopic transplantation is recommended as the primary choice for fertility restoration due to better overall pregnancy and live birth outcomes, while heterotopic transplantation can be considered when pelvic or intra-abdominal surgery is prohibitive, or when only restoration of ovarian endocrine hormone restoration is desired.[65] For females with hematologic malignancies or cancers with a high risk of ovarian metastasis, OTT may not be recommended. There are ongoing efforts to develop and improve in vitro growth and maturation of oocytes of all stages to expand the fertility potential of cryopreserved ovarian cortical tissue.[66]

Current reports indicate upwards of 290 live births from OTT in patients who were post-pubertal at the time of tissue procurement.[60] In large European OTT cohort studies, rates of successful pregnancy after OTT ranged from 30% to 37%, with live birth rates from 28% to 34.5%.[58,60,67] Spontaneous conception occurred in 40%–69% of patients who achieved pregnancy, with 36%–50% requiring assisted reproductive technology (ART).[58,60] Women who required ART after OTT had lower live birth rates than those who conceived naturally after OTT.[68] Live birth rates after the use of vitrified oocytes are reported around 32%.[67] Most women experience hormone restoration within 4–5 months of OTT, with a median graft survival of 2.5 years.[58,60,67]

Children who receive high-dose pelvic radiation may not be candidates for OTT given the significant risk of pregnancy-related complications associated with uterine irradiation.[58] However, patients may choose to build a family via use of their preserved tissue and a surrogate. Patients who have received a previous course of chemotherapy can be offered OTC, as chemotherapy before OTC is no longer a contraindication to tissue freezing.[58,60,69] Chemotherapy prior to OTC may affect follicle survival after OTT, but rates of resumption of overall ovarian function and pregnancy between patients who received chemotherapy and those who did not, did not vary significantly.[58] However, patients who received alkylating chemotherapy as part of their treatment had lower rates of pregnancy when compared to women who received non-alkylating chemotherapy.[58]

TABLE 2 Options for fertility preservation for male patients.[75]

	Details	Pros	Cons
Sperm cryopreservation	Semen is collected, processed and sperm is frozen for use in the future	• Standard of care • Quick and easy	• Only for pubertal/post-pubertal • May need multiple collections • Some specific conditions are ideal (abstinence before, transport time, and temperature, etc.)
Testis biopsy and cryopreservation	The testis is biopsied directly. If present, sperm are extracted and then frozen for future use. If no sperm are present, tissue can be cryopreserved for future technology that may enable its use for reproduction	• For pre-pubertal and post-pubertal patients • Can be combined with another surgical procedure	• Requires surgical procedure
Electroejaculation	A machine is used to induce ejaculation on those who cannot collect a semen sample by conventional methods	• Allows for mature sperm collection • Can be combined with another surgical procedure	• Requires special equipment • Requires anesthesia • Only for pubertal and post-pubertal patients
Sperm extraction	Sperm are extracted surgically from testis or epididymis and frozen	• Reserved for those who do not have sperm in semen sample collected by conventional methods	• Only for pubertal/post-pubertal patients • Invasive procedure • Requires embryologist on site

A systematic review of fertility preservation procedures performed in patients 20 years of age and younger at the time of oocyte or ovarian tissue harvest has been performed. At the time of the review, 1019 children had undergone OTC and 20 oocyte cryopreservation. Of those patients, 18 underwent OTT and two patients underwent oocyte reimplantation. Of the 18 who underwent OTT, 16 had tissue transplanted for fertility reasons and two for pubertal transition. There was a 69% pregnancy rate and 56% live birth rate after OTT, with 60% of live births conceived spontaneously. Two live births were reported from children who had their ovarian tissue procured pre- or peri-pubertal.

4 | MALE FERTILITY PRESERVATION

4.1 | Fertility preservation options for males

For post-pubertal males who are able to ejaculate, there is a clear standard of care for sperm cryopreservation. This has long been established as successful for the future use with intrauterine insemination (IUI) or intra-cytoplasmic sperm injection (ICSI). Additionally, this approach is typically the easiest for the patient and has the fewest logistical hurdles. For pre-pubertal male patients, and those post-pubertal patients who cannot produce a masturbated ejaculate with sperm, a surgical procedure is required. Ideally, such a surgery will be combined with another procedure (central line placement or tumor resection). The associated time pressure of fertility preservation often factors into decisions made by patients and families. Current fertility preservation options for male patients are summarized in Table 2 and Figure 4.

Of note, post-pubertal males are generally defined as Tanner stage ≥3,[70] corresponding to a testicular volume of ≥6 cm^3.[71] Therapy-related impaired spermatogenesis, testosterone deficiency, hypogonadotropic and hypergonadotropic hypogonadism may all lead to infertility in this population. In pre-pubertal males, the primary option for fertility preservation is testicular biopsy with cryopreservation of this tissue in hopes of future technology that will enable in vitro or in vivo maturation of these tissues to the point that they could be used for producing an embryo.[72–74] Additionally, for post-pubertal males who cannot produce a masturbated ejaculate, electroejaculation can be considered. However, due to the invasive nature of the procedure, many times surgical retrieval of sperm is preferred.

4.2 | Testicular tissue biopsy for cryopreservation

Generally, trans-scrotal access to the testis is utilized aside from rare instances of surgically obtaining normal seminiferous tubules from a "malignantly affected gonad" at the time of an orchiectomy for a primary testicular or para-testicular tumor, during which an inguinal approach is used as part of the orchiectomy. Making a relatively small incision in the scrotal skin and tunica vaginalis permits direct vision of the tunica albuginea. To avoid damage to the peripheral vascular supply of the remaining portion of the testis being biopsied, a transverse incision is then made in the tunica albuginea and the seminiferous tubules are extruded and can be sharply or bluntly dissected free from the remaining part of the testis. Depending on the protocol, a specific volume of seminiferous tubules may be required. This tissue

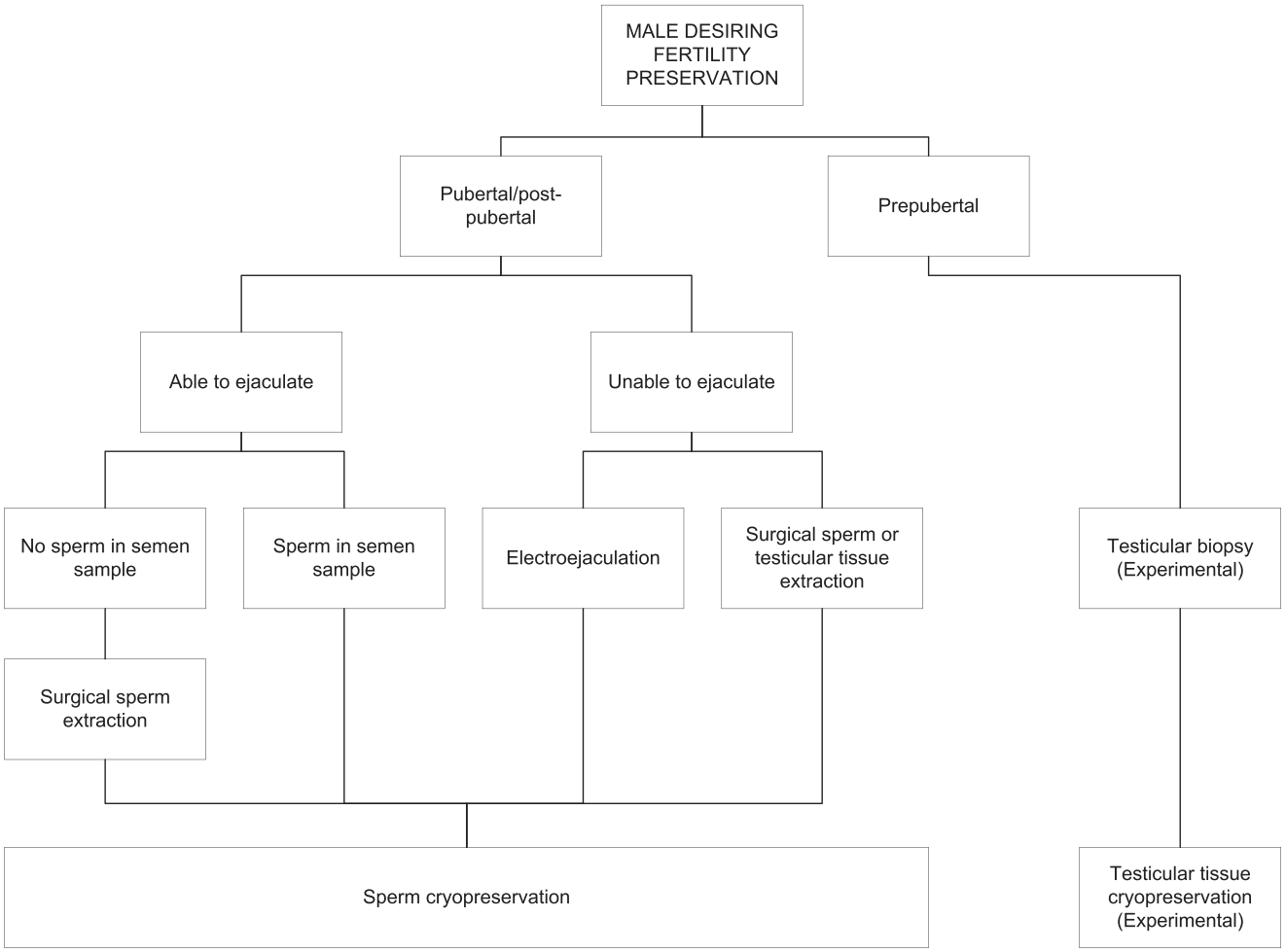


FIGURE 4 Flowchart of options for fertility preservation in male patients.

is then handed off for further processing by pathology, to determine if it is free of malignancy, and then by the laboratory personnel for cryopreservation. For patients with a borderline pubertal status, the laboratory can investigate for any rare, isolated sperm that, if present, can be specifically cryopreserved in addition to cryopreserving the tissue.

5 | CONCLUSION

With advances in multimodal therapy for children and adolescents with cancer over the last several decades, long-term survival is expected in the majority of patients. The burden of therapy-related comorbidities must be anticipated and addressed at diagnosis, including fertility challenges related to treatments. As risks of therapy become more elucidated, refined, and reduced when feasible, and as reproductive-assisted technologies continue to advance, options for fertility preservation at diagnosis, during therapy, and long after cure should be discussed and offered as part of multidisciplinary, comprehensive cancer care for all children.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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