



Fertility Preservation for Children and Adolescents: An Update Covering Recommendations for Cisgender and Transgender Youth

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Abstract

Fertility preservation is a rapidly expanding interdisciplinary field, with new technologies available in the last few years and increasing press coverage. The topic of fertility preservation for the pediatric population is especially crucial for appropriate healthcare providers to understand in order to maximize timely access to care for patients. This review will compile the most recent practice guidelines on fertility preservation from multiple clinical societies, as well as highlight considerations specific to pediatric patients undergoing fertility preservation prior to treatment for malignancies or gender-affirming therapies.

Abbreviations

ACOG: American College of Obstetrics and Gynecology; AFAB: Assigned Female at Birth; AMAB- Assigned Male at Birth; AMH: Anti-Mullerian Hormone; ASRM: American Society for Reproductive Medicine; FP: Fertility Preservation; GAT: Gender-Affirming Therapy; GD: Gender Dysphoria; GnRH: Gonadotropin-Releasing Hormone; IVF: *In Vitro* Fertilization; IVM: *In Vitro* Maturation; OTC: Ovarian Tissue Cryopreservation; PA: Pediatric and Adolescent; TBI: Total Body Irradiation; TESE: Testicular Sperm Extraction; TTC: Testicular Tissue Cryopreservation

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Introduction

The clinical, scientific, ethical, and legal aspects of Fertility Preservation (FP) have been extensively studied and are fairly well established in clinical practice for adults. However, techniques and guidelines for FP in children and adolescents are less straightforward. Two main factors complicate the consideration of FP in the Pediatric and Adolescent (PA) population as compared to adults: collection of gametes from pre-pubertal children, and the role of patient autonomy when decisions must be made by both the parent or guardian and patient.

While adults generally choose to preserve gametes before undergoing gonadotoxic therapy for medical conditions or to bypass the age-related fertility decline in women, indications for FP in PA patients are considerably more varied. FP is essential to protect reproductive potential in young patients undergoing high-risk gonadotoxic treatment for malignancies, but it is also important for conditions necessitating bone marrow transplant, including sickle cell disease, rheumatologic conditions, hypogonadic genetic syndromes such as Klinefelter and Turner syndromes, and in young patients with gender dysphoria considering definitive Gender-Affirming Therapy (GAT) [1-4].

We will summarize currently available options for FP for the Pediatric and Adolescent (PA) population and review the latest clinical practice guidelines for FP in PA patients across several clinical societies. We will also discuss considerations specific to PA patients undergoing gonadotoxic therapies for malignancy and gender transition. In order to be inclusive of all gender identities while discussing the biological aspects of fertility, we will refer to cisgender males and transgender females as Assigned Male at Birth (AMAB), and cisgender females and transgender males as Assigned Female at Birth (AFAB).

Fertility Preservation for Patients Assigned Female at Birth

Options for FP in AFAB patients is a rapidly expanding field, with multiple updates in clinical guidelines in the last year. Oocyte cryopreservation and Ovarian Tissue Cryopreservation (OTC) are the two main options for this population (Figure 1A). FP should ideally be done before initiation of therapies at high-risk for gonadotoxicity, although even treatments considered low-risk have been shown to have detrimental effects on ovarian follicles [5]. Embryo cryopreservation, the proven method with the highest likelihood of live birth [6,7], is less applicable for PA patients than for adults, and thus will not be discussed in-depth.

Oocyte cryopreservation

In post-pubertal females, ovarian stimulation with mature oocyte cryopreservation remains the most proven and effective method of FP. It can generally be attempted if an adolescent is post-menarchal, although at least one case report describes successfully retrieving mature oocytes after Controlled Ovarian Hyperstimulation (COH) in a pre-menarchal adolescent [8].

COH involves gonadotropin injections in order to stimulate follicle growth, conventionally beginning with the follicular phase of the menstrual cycle. Multiple studies have shown that COH is safe, effective, and does not significantly increase the time to treatment in either adults or adolescents with cancer [9,10]. As the delay in time to treatment due to the conventional method of beginning COH with the follicular phase has been a significant concern for both patients and providers, it has been shown that random-start COH can shorten the time necessary for oocyte retrieval and yields comparable numbers of oocytes to the conventional protocol [7,11].

Ovarian tissue cryopreservation

As of the most recent guidelines published in 2019, the American Society for Reproductive Medicine (ASRM) no longer considers OTC experimental [6]. This represents a major accomplishment for the field of FP and especially for the PA population, as OTC is an option for pre-pubertal AFAB patients as well as post-pubertal patients who are not candidates for ovarian stimulation. Given that OTC is a relatively new option for FP, few pre-pubertal patients who have cryopreserved tissue have reached the age of desired reproduction, and there are limited live-birth outcomes in this population. ASRM cites that approximately 130 live births have resulted from transplantation of ovarian tissue collected after puberty [6], and at least one from ovarian tissue cryopreserved before menarche [12].

OTC is a more versatile procedure than collection of individual oocytes. The tissue can be collected at the time of surgical treatment for malignancy, and therefore usually does not significantly delay treatment of the underlying condition [13]. Complete unilateral oophorectomy is recommended in pre-pubertal patients to increase the number of follicles included in the sample, while partial oophorectomy may be sufficient for post-pubertal adolescents [14]. For patients undergoing cystectomy or partial oophorectomy for ovarian masses, normal-appearing ovarian tissue can be identified around the mass and preserved [13,14]. When the patient desires fertility, orthotopic transplantation into the original location in the pelvis can result in resumption of ovarian endocrine function, regular menstrual cycles, gamete maturation, and the possibility of spontaneous pregnancy [12,14,15]. Alternatively, the tissue can be transplanted into a heterotopic site if the pelvis is not an

ideal environment from scar and adhesion formation or previous irradiation. Heterotopic transplantation has been shown to restore endocrine function and menstruation, but reproductive options are limited to *In Vitro* Fertilization (IVF) [16]. Although endocrine function has been shown to return for at least seven years after either type of transplantation, it is not recommended to transplant the ovarian tissue back into the patient until they are ready to conceive because there are not yet adequate studies on the duration of oocyte viability after tissue cryopreservation [6].

In addition to freezing ovarian tissue, immature oocytes can be aspirated from antral follicles and vitrified, or matured with *In Vitro* Maturation (IVM) before cryopreservation [14,17]. IVM has been shown to be feasible and effective after ovarian tissue removal in all stages of the menstrual cycle, with no difference in oocyte retrieval, maturation or fertilization rates when collected in the follicular or luteal phases [18]. The combination of both OTC and oocyte aspiration with immature oocyte cryopreservation or IVM with mature oocyte cryopreservation has been proposed to maximize future options in PA patients [14]. Notably, while one study found that children and adolescents who had not yet gone through chemotherapy had higher numbers of immature oocytes collected from harvested ovarian tissue and higher maturation rates of these oocytes after IVM than patients who had already undergone gonadotoxic therapy, sufficient numbers of oocytes were also collected and matured from post-treatment patients, highlighting the versatility of the combination of OTC and IVM [14].

A major advantage of OTC is the elimination of the need for COH and transvaginal oocyte retrieval, as in oocyte cryopreservation, which can delay treatment and is often logistically difficult for pediatric patients. The most significant risk of OTC is the possibility of malignant cell reseeding after tissue transplantation back into patients with ovarian cancer or hematologic malignancies. Oocyte aspiration from the tissue and IVM is one method to avoid this.

Fertility Preservation for Patients Assigned Male at Birth

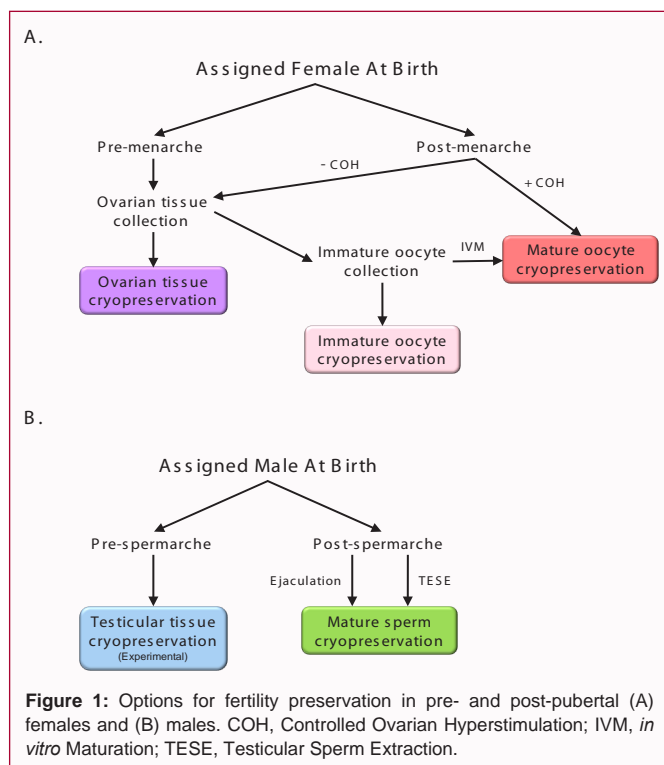
Methods of FP are much more limited in AMAB patients, especially those who are pre-pubertal, than in AFAB patients. Mature sperm cryopreservation is the only established option, while Testicular Tissue Cryopreservation (TTC) is considered experimental (Figure 1B).

Sperm cryopreservation

Cryopreservation of mature sperm is the optimal FP method for the post-pubertal AMAB population [6,19]. The average age of spermarche is estimated to be between 12 years to 14 years [20]. While collection of ejaculated semen is the simplest method, there may be barriers to ejaculation, including but not limited to patient comfort, especially in transgender individuals, hypogonadism, neurological problems, or medication side effects. Methods to induce ejaculation in patients with neurological injuries include penile vibratory stimulation or electroejaculation [6]. Alternatively, in patients who have reached spermarche but are not able to ejaculate or have insufficient sperm in the ejaculate, Testicular Sperm Extraction (TESE) can provide adequate sperm amounts to cryopreserve [6,21].

Testicular tissue cryopreservation

For pre-pubertal AMAB patients who have not reached spermarche, the only option for FP is TTC. Testicular biopsy prior to TTC can also determine if mature sperm are present in the tissue,



which can then be cryopreserved similar to TESE methods [6]. TTC is still considered experimental and thus all patients must be enrolled in an IRB-approved clinical trial [6]. There have been no live human births from TTC reported to date; however, animal models of this technique are promising, with the recent birth of the first non-human primate conceived with sperm extracted from testicular tissue harvested from pre-pubertal rhesus macaques, cryopreserved, and reimplanted back into the animals [6,22]. Multiple academic centers are actively enrolling pre-pubertal AMAB patients into clinical trials involving TTC in anticipation of future advancement of these technologies [23-26].

Considerations for Specific Populations

Pediatric and adolescent cancer patients

As pediatric cancer treatments improve, more consideration must be given to preparing for long-term quality of life after treatment. From 2009 to 2015, five-year survival rate for all cancers in children and adolescents ages 0-19 years was 85.7%, increased from 61.5% from 1975 to 1977 [27]. The three mainstays of cancer treatment—chemotherapy, radiation therapy, and surgery— all have significant impacts on reproductive potential in both pre- and post-pubertal patients [28-30]. All oncology patients should be counseled on the risk of gonadotoxicity of the specific proposed treatment, and patients at high-risk for infertility should be referred to a fertility specialist for discussion of FP options [7,31]. While FP before any gonadotoxic therapy is ideal, FP often occurs only after treatment initiation, whether due to initial patient or family refusal or lack of provider-initiated counseling [32,33]. FP after gonadotoxic therapies is also possible and should continue to be offered to patients [6,7,28,31]. Additionally, ASRM emphasizes the importance of continued discussions about fertility and reproductive health throughout treatment and in survivorship programs [31].

Patients undergoing high-risk gonadotoxic therapies who do not wish to cryopreserve oocytes can consider medical or

surgical protection of the reproductive organs. For AFAB patients undergoing targeted pelvic radiation, oophorectomy can transpose the ovaries away from the field of radiation [28]. Alternatively, ovarian or testicular shielding can protect the reproductive organs during Total Body Irradiation (TBI). One case study has reported a pre-menarchal 11-year-old girl who underwent TBI with ovarian shielding, with subsequent spontaneous menarche at age 14 and spontaneous pregnancy at age 23, highlighting the effectiveness of this relatively simple intervention [34]. For post-pubertal AFAB patients being treated with high-risk chemotherapies, co-treatment with Gonadotropin-Releasing Hormone (GnRH) agonists can induce ovarian quiescence and may decrease the risk of toxin-associated ovarian insufficiency [6,28,35], as well as being frequently used to suppress chemotherapy-induced heavy menstrual bleeding [36]. However, there is conflicting evidence about the clinical utility and effectiveness of GnRH agonist therapy for FP, and guidelines suggest counseling patients on the limited knowledge about this option [6,7,35]. The American Society of Clinical Oncology (ASCO) recommends that GnRH agonist therapy only be offered as FP to post-pubertal females in whom oocyte retrieval or OTC are not options, but not in place of proven FP methods [7]. Additionally, GnRH analog therapy has not shown to be effective for FP in AMAB patients, and is not recommended by ASRM or ASCO [6,7].

Transgender children and adolescents

Guidelines from ASRM, the American College of Obstetricians and Gynecologists (ACOG), the Endocrine Society, and the World Professional Association for Transgender Health (WPATH) recognize the lack of data regarding the counseling and health management of children and adolescents diagnosed with Gender Dysphoria (GD). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes different criteria for the diagnosis of GD in children or in older adolescents and adults, recognizing that rates of persistence of GD from childhood into adolescence are generally low [37]. Close follow-up of children with GD by healthcare providers is essential to monitoring mental and physical health, as well as assessing desires for Gender-Affirming Therapies (GAT).

The two foundations of medical GAT for transgender patients are pubertal suppression, usually with a GnRH agonist, and cross-sex hormone therapy [19,38,39]. GnRH agonist therapy is fully reversible, and while it temporarily impairs gamete production and maturation, several studies have shown a return of Anti-Mullerian Hormone (AMH) levels in AFAB patients and male testosterone levels and normal semen parameters in AMAB patients [38,40], although the majority of these studies have been conducted in children with precocious puberty or other endocrine disorders as opposed to GD [41,42]. Furthermore, GnRH agonist therapy has been shown to be safe for the long-term health of peri-pubertal children [43,44]. Multiple guidelines suggest that pubertal suppression with GnRH agonists should be the first-line treatment for GD in peri-pubertal children in order to allow the patient time to explore their gender identity and consider the desire to pursue a more permanent physical transition [19,38,39,45].

While pubertal suppression is a useful, reversible method, particularly in the PA population, cross-sex hormone therapy is largely irreversible and has permanent effects on fertility. In contrast to the reversible effects of GnRH on AMH levels, testosterone treatment has been shown to strongly and permanently suppress AMH in transgender male AFAB patients [38,39,46]. Similarly, persistent

azoospermia was observed in semen samples of a transgender female AMAB patient who had undergone 2 years of feminizing therapy with estradiol and spironolactone [40]. Thus, it is crucial for health care providers to thoroughly counsel transgender children and adolescents and their families about FP before beginning cross-sex hormone therapy.

In addition to the ethical considerations about consent presented above, parents and patients must be aware about the lack of definitive data or guidelines about FP specific to the transgender population [45]. While all of the options previously described can be offered to patients based on the pubertal status, the ASRM Ethics Committee, the ACOG Committee on Adolescent Health Care, and WPATH suggest that transgender patients delay gonadectomy as definitive surgical GAT until adulthood [19,39,45]. At that time, it may be possible to isolate oocytes from ovarian tissue as described above for FP.

General Aspects of Counseling

Despite the collective agreement across specialties that discussion of FP is imperative in the pre-treatment counseling, ideally occurring at the first visit with any provider in which gonadotoxic therapies are presented, the percentage of times this counseling actually occurs is suboptimal [32,33,47-49]. Providers have cited that barriers to initiating FP discussions with their patients include insufficient training in fertility counseling for non-specialists, consideration of infertility as a secondary concern during treatment for a life-threatening medical condition, especially in the PA population, not wanting to overwhelm patients with too much information at once, perceived financial burden to patients, and the lack of a standardized algorithm for referral and counseling [49,50]. However, there is overwhelming evidence that patients and families faced with the possibility of sub-fertility from any cause or treatment want healthcare providers to discuss FP as early as possible [7,33,51-56]. Studies have found that patients and families who recall having a discussion about FP with any healthcare provider, with subsequent referral to a fertility specialist, have lower rates of decision regret. Furthermore, patients and families identified not having FP counseling initiated by a physician in a timely manner as a main source of dissatisfaction [52]. Thus, guidelines recommend that providers in any specialty, including primary care medicine or pediatrics, medical and surgical oncology, gynecology, urology, endocrinology, and psychology, be prepared to counsel patients on this topic and refer to an appropriate FP program [6,19,28,31,57]. In the adolescent population, care should be taken to counsel the patient and parents both separately and together about FP options, and risks and benefits of each method, as well as providing written information, in order to maximize their comfort and autonomy [31,45].

While consent of the parent or guardian is crucial, children and adolescents must give assent for FP, in accordance with the American Academy of Pediatrics' (AAP) policy statement on pediatric assent [7,58]. In children too young or unable to give assent, parents' wishes should be considered to be in the best interest of the child. However, multiple guidelines suggest that if the patient is considered able to assent, FP should not be done with the patient's objection, regardless of the parents' wishes [31,59].

The disposition of the preserved gametes, should the patient choose not to use them or die before use, should be incorporated into consent documents at the time of preservation. It should be

clear to patients and parents that these instructions can be amended at any time, and should be updated with the patient's wishes when they reach the age of majority [31]. One study found that when young women who had cryopreserved oocytes before gonadotoxic therapies were given the choice between donating to research, donating to an individual for pregnancy, or discarding the oocytes, there were not significant differences in the choices of individuals older or younger than 18 years, highlighting the ability of adolescents to make similar informed choices as young adults [10]. In accordance with this principle of patient autonomy, guidelines suggest that parents do not have the right to use their child's preserved gametes if the child dies before adulthood and the gametes should be discarded [59], although this is a topic of ongoing debate. Providers should not hesitate to consult the hospital's ethics committee when necessary.

In both populations considered, the cost of FP is often perceived as one of the most limiting factors. The cost of FP includes not only the initial collection and processing of the sample, but also storage fees until the patient is ready to reproduce, which can be up to several decades for patients in the PA population. This extra cost, which is usually not covered by health insurance, comes at a time when families are already burdened by bills for medical or surgical treatments for their condition. Recently, state governments in the United States have begun to implement and expand mandated FP insurance coverage, which is promising but has much room for improvement in inclusivity for all medical indications for FP [60]. Programs such as LIVESTRONG Fertility, previously Sharing Hope, are available to cancer patients to cover costs of oocyte, sperm, and embryo cryopreservation, as well as providing free medications for ovarian stimulation. While a recent study shows that LIVESTRONG utilization rates have risen exponentially since implementation in 2004, the percentage of eligible cancer patients who receive financial assistance is extremely low, less than 3% for both males and females [61], which has been speculated to be because FP procedures are cost-prohibitive despite this assistance.

Conclusion

Technologies for fertility preservation in the pediatric and adolescent populations have improved rapidly in recent years, with updated clinical guidelines suggesting broader use of FP for appropriate populations. Timely counseling and referral to an FP specialist is desired by patients and their families and clearly results in better outcomes. Additionally, more robust data and recommendations for FP in populations such as transgender children and adolescents are needed in order to expand the reach of these important services.

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