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REVIEW

Fertility Preservation in Children and Adolescents: Where We Are and Where We Are Going

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Abstract

Purpose of Review This review will describe current pediatric and adolescent fertility preservation methodologies and the ethical concerns surrounding these procedures, as well as highlight recent research that may pave the way for the development of new fertility preservation options.

Recent Findings Research is ongoing to allow prepubertal patients, particularly those with testes, to be able to have biologic children in the future. Studies on sperm in vitro maturation highlight the importance of supporting the spermatogonial stem cell niche for the development of mature sperm. The live birth of a rhesus macaque from in vitro fertilization using prepubertal testicular tissue and in vivo matured sperm gives hope to future human births. For patients with ovaries, prior work has led to successful fertility but further research is underway to refine these techniques and optimize outcomes. Organoid scaffolds have shown promise when being used for in vitro oocyte maturation.

Summary For children and adolescents undergoing gonadotoxic treatment, such as chemotherapy, or hormonal treatment, such as gender-affirming hormone therapy, future fertility potential may be negatively impacted. It is recommended that fertility preservation (FP) be offered to these patients and families prior to undergoing treatment. Fertility preservation for postpubertal patients mimics that in adults. For prepubertal children, however, the options are limited and in some cases still experimental. It is essential that this work continues so that we may offer children and adolescents the right to an open future and preserve their fertility potential.

Keywords Pediatric oncology · Fertility preservation · Transgender medicine · In vitro gamete maturation

Introduction

For children and adolescents undergoing gonadotoxic treatment, such as chemotherapy, or hormonal treatment, such as gender-affirming hormone therapy (GAHT), future fertility potential may be negatively impacted. Though these conditions may seem vastly different, the potential treatments often have the same detrimental impacts on fertility; as such, it is recommended that fertility preservation (FP) be offered to these patients and families prior to undergoing treatment. Though this review focuses on patients with oncologic diagnoses or those undergoing GAHT, the concepts apply to other conditions, such as sickle cell anemia and ulcerative colitis, which require potentially spermatoxic medications. While the psychosocial issues related to FP in these populations may be different, the science of FP is very much the same. Notably, FP may be the norm in adults undergoing similar therapies; however, the developmental and social factors of children and adolescents as well as their parents make FP far less common in these younger populations. The process of FP for postpubertal patients mimics that of adults. For prepubertal children, options are limited and in some cases considered experimental. Research is ongoing to allow prepubertal patients, particularly those with testes, to be able to have biologic children in the future. For patients with ovaries, prior work has led to successful fertility but further research is underway to refine these techniques and optimize outcomes. It is essential that this work continues so that we may offer children and adolescents the right to an open future and preserve their fertility potential. This review will describe current fertility preservation methodologies and the ethical concerns surrounding these procedures, as

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well as highlight recent research that may pave the way for the development of new fertility preservation options.

Current Practice Recommendations

A Team Approach

Though guidelines recommend all patients undergoing treatments that will potentially affect fertility be educated on the risks and offered FP, in practice, this is not always the case [1, 2]. While there are understandable barriers to completing FP, there should be no child or family who is not offered a clear discussion of the risks and options. Adult studies show that patients and families who have undergone therapies deleterious to fertility have higher rates of regret if they did not receive fertility-specific counselling and did not engage in an active choice regarding FP [3–5]. A multidisciplinary team approach is essential to ensuring this active choice. Besides the treating endocrinologist or oncologist, this team should include social work, nursing, mental health providers, fertility specialists, and a fertility navigator. Integration of fertility specialists into inpatient teams and outpatient clinics is essential to ensuring families receive dedicated, timely, and comprehensive information regarding FP options and potentially increases the number of patients pursuing FP [6, 7]. Though a dedicated fertility navigator may be a resource challenge for a small program, recent work has shown that the addition of a navigator markedly increases fertility consultations [8]. Previous work from adults also shows an increase in patient satisfaction [9]. Smaller programs can utilize an interested nurse, advanced practice provider, or social worker as a fertility liaison while they grow their resources. An integrated, multidisciplinary team including fertility specialists is critical to the comprehensive care of young patients undergoing gonadotoxic or fertility suppressive treatments.

Available Fertility Preservation Options

For the purposes of this discussion, we will refer to patients with testes and patients with ovaries rather than use gendered terms such as male and female. A summary of FP options can be found in Fig. 1.

Options for Patients with Testes

Postpubertal

Cryopreservation of sperm was first pioneered in the 1950s and has been used successfully for live births since that time [10]. This is by far the most common method of FP in postpubertal patients with testes. Obtaining a sample is fast and noninvasive. Frozen sperm can produce similar rates of live births when compared with fresh sperm [11]. The principal concern regarding sperm cryopreservation in adolescents and young adults is the means in which a sample is obtained. Typically, for adolescent patients, this is done at home and then transported to a cryopreservation lab, rather than producing a sample at the lab. For hospitalized patients, this can be done in the hospital and then transported by family members or a courier. Federal regulations require HIV testing for storage, and local facilities may also require hepatitis B, hepatitis C, and syphilis testing. This is done to prevent inadvertent transmission among samples. For patients who are peripubertal and willing to try, we recommend masturbation and attempted cryopreservation. A recent study from our institution showed that a child in Tanner Stage 3 with 12-mL testes successfully cryopreserved from a masturbated

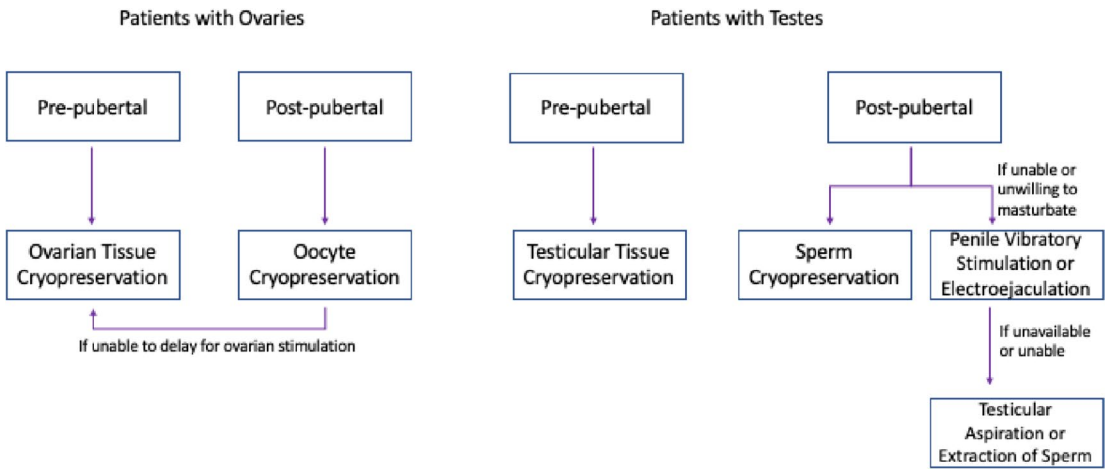

Fig. 1 Pathways for fertility preservation

specimen [7]. This is consistent with prior work showing viable sperm in biopsied specimens of patients with testes 10–12 mL but has the advantage of lower cost and avoiding a procedural intervention [12]. Costs vary widely by practice and location but typical costs are $150–$500 for initial processing and preservation and yearly storage varies from $300 to $1000 (Table 1).

A potential barrier to sperm cryopreservation is the patient's inability, or unwillingness to masturbate. This may be due to embarrassment, stress, developmental delay, religious proscription, or dysphoria. Electroejaculation or penile vibratory stimulation can be suggested for these patients. Electroejaculation is not widely available outside of fertility centers and requires the use of general anesthesia. Insertion of a probe into the rectum and electrical stimulation causes seminal emission and ejaculation. Costs vary from $10,000 to $12,000 [13]. Studies have shown that the sperm collected may have decreased motility, concentration, and volume or may not be collected at all, further limiting the utility of this avenue for preservation [14, 15]. Penile vibratory stimulation has been used in adults with spinal cord injuries and can in theory be used in adolescents and young adults, but use and success of penile vibratory stimulation in this population are limited in published literature [16, 17]. Lack of familiarity with and access to penile vibratory stimulation effectively limits its use pediatric centers in the United States but it should be considered where available.

If electroejaculation or penile vibratory stimulation is unavailable and undesirable or has failed, patients can pursue a testicular aspiration or extraction of sperm. In adults, these can be done awake under local anesthesia but in the pediatric population, these are surgical procedures under general anesthesia. These can be done at the time of bone marrow biopsy or port placement for patients with oncologic diagnoses. This will potentially decrease the cost of anesthesia. Costs vary from $2500 to $8000 based on procedure, facility, and region. Surgical specimens must be transported to a cryopreservation lab and processed for storage. Testicular extraction of sperm can also be done at the time of gender-affirming surgical therapy in the future but patients should be counselled on high rates of subfertility or infertility with abnormal semen parameters [18].

Prepubertal

At this time, the only option for FP for prepubertal patients with testes is testicular tissue cryopreservation (TTC) with hopes for future in vitro maturation. This has not yet been shown in humans and as such is considered experimental. This will be further discussed in the "Innovations" section. Prepubertal transgender patients must be counselled that while the fertility effects of pubertal suppression and GAHT are thought to be reversible, this can take months and there is limited long-term data on future sperm quality. During those months, they will need to be off of hormone therapy and may see undesired masculinizing changes. As TTC is considered experimental, it is less likely to be covered by insurance, even in states that mandate fertility coverage. Costs range from $2500 to $8000 for the procedure (Table 1). Storage will be another $300–$500 per year. The costs to mature the sperm are as yet unclear, as is the efficacy.

Options for Patients with Ovaries

Postpubertal

Postpubertal FP for patients with ovaries can be done via oocyte cryopreservation, or ovarian tissue cryopreservation (OTC). OTC is discussed further in the prepubertal section. Oocyte cryopreservation requires 1–2 weeks of ovarian stimulation for optimal oocyte harvesting, which may delay treatment [19]. This can be of concern for chemotherapy. While often the family and oncology team can devise a reasonable plan for delay, this may not be recommended for certain patients and cancers. Costs range from $12,000 to $20,000 for the initial process but it should be discussed that use of preserved oocytes will require in vitro fertilization in the future, which can add another $12,000–$15,000 in the future [13]. As with all cryopreservation, there is also a yearly storage fee, ranging from $300 to $1000.

For transgender patients, ovarian stimulation may cause short-term feminizing effects and as such be undesirable. Aromatase inhibitors may lessen these effects. Ovarian stimulation is also typically done after menstruation. Menstruation can cause significant dysphoria for some transgender patients. As there have been several transgender men who have

Table 1 Approximate costs of fertility preservation (based on pricing in the New York Section of the American Urological Association)

Fertility preservation technique	Costs of collection and processing (including anesthesia and surgery when required)
Sperm cryopreservation (masturbated specimen)	$150–$500
Electroejaculation	$10,000–$15,000
Testicular tissue cryopreservation	$2500–$8000
Mature oocyte extraction	$10,000–$15,000
Ovarian tissue cryopreservation	$12,000–$20,000

successfully achieved pregnancy after several years of GAHT, most patients will choose not to pursue oocyte cryopreservation or OTC; however, some data suggests low oocyte yield after hormonal therapy and long-term effects on offspring are not well described [20–22].

Prepubertal

The current standard for prepubertal children and adolescents with ovaries is cryopreservation of a whole ovary or strips of ovarian tissue with plan for future autotransplantation. Similar to TTC, this requires surgical excision or biopsy under general anesthesia. There have been over 100 live births using ovarian tissue cryopreservation. As of 2019, this is no longer considered experimental and should be offered to patients and families [23]. In practice, FP via OTC is limited to centers with access to slow freezing or vitrification processes [24]. Vitrification (essentially, fast freezing) is used less commonly than slow freezing. OTC does require a gynecologic or pediatric surgeon for tissue harvesting. This can be done as young as infancy. Costs range from $10,000 to $15,000 (Table 1).

There is a theoretical concern that malignant cells may be harvested unintentionally if present in the ovary. If this were the case, transplantation in the future may trigger a relapse. This is a particular concern for leukemia and lymphoma and is less of a concern for solid organ cancers. Because of this, some centers refrain from OTC in patients with leukemia or lymphoma while others recommend once cycle of chemotherapy prior to tissue harvesting. Some authors recommend washing the tissue prior to autotransplantation to remove malignant cells but others have transplanted without this method and have not shown relapse [25, 26]. Studies looking at the tissue at the time of excision have not seen malignant cells in the tissue [27]. We recommend a thorough discussion of the risks and options.

When fertility is desired, the ovary is autotransplanted. This can be done orthotopically or can be done just under the abdominal wall to allow for transabdominal oocyte harvesting. Transplantation has shown great success and several live births [28, 29]. Future autotransplantation of an ovary or ovarian tissue may not be desired for transgender patients given the hormonal effects. To our knowledge, there has not been a report of transplantation into a surrogate. This may be possible but would likely require immunosuppression.

Ethical Considerations

There are several ethical issues that arise in FP for children and adolescents. To begin, it may be uncomfortable for pediatric patients to even engage in conversation on their fertility and parents may not wish to subject their children to such a discussion. Even requesting an adolescent to masturbate in order to provide a sperm sample may be considered controversial, particularly in some religious communities. In a recently reported study, children undergoing gonadotoxic therapies were polled for their knowledge and interest on FP [30]. Results showed that many children are aware of how their treatment can be detrimental to their future fertility. Additionally, while many children expressed that they were worried about the cost or pain of FP treatment, the general response to education on the topic was a positive one. Therefore, we recommend age-specific and developmental specific education regarding fertility considerations and options for preservation. Child life and social work can be particularly helpful partners in this endeavor. Embarrassment, unease, or lack of familiarity with options is not an acceptable reason as to not discuss FP with patients and families.

Another ethical consideration is that of time. Despite our best efforts, FP may delay treatment, be it by hours or weeks. This delay may not be acceptable to patients, families, or their treating physicians. Patients awaiting pubertal suppression or GAHT may develop irreversible undesired secondary sex characteristics that will necessitate future surgical intervention. They may also experience worsening dysphoria and mental health while awaiting FP and delaying GAHT. For patients with oncologic diagnoses, a delay in treatment may result in poorer long-term outcome. In these cases, a delay is often unacceptable to patients, families, or treating physicians. When time is of the essence, it is essential to balance the risks and benefits of FP and critical that we provide all the available information to patients and families so that they may engage in shared decision-making.

As with any type of pediatric patient, the input and influence of their parents must be considered in the decision-making process. This is particularly poignant in patients with a poor oncologic prognosis. If the patient has a limited chance of survival, cryopreservation is not for them, but for their families. Legally, the ownership of gametes harvested from a pediatric patient resides with the parents. Some will argue that posthumous reproduction should be allowed as the act of cryopreservation assumes that the person they came from was intending on having children [31]. For children and adolescents undergoing cancer treatment or gender affirmation, this assumption is less clear as cryopreservation is being often done as a precautionary measure. To our knowledge, posthumous use of gametes obtained from a minor has not occurred. There has been precedent set in which parents have used the gametes of their deceased adult children to have grandchildren [32, 33]. This poses an ethical quandary and without a clear discussion should be considered unacceptable for gametes of children and adolescents. Given that patients under the age of 18 are legally allowed to

make decisions on other reproductive health issues, they should be involved making the decision on what should be done with their gametes if they were to die. This can be an even more challenging topic than that of FP itself. Ideally, families would create an advanced directive that details the child's wishes; however, in the cases of imminent chemotherapy, there is often no time for this legal document. If there is no clear directive, we advise against parents using cryopreserved tissue from their child posthumously and recommend disposal upon the patient's death. As use for reproduction cannot be assumed, neither can use for research.

Cost is a significant barrier to FP and poses further ethical considerations. Table 1 summarizes approximate costs for FP options [13, 34]. There are wide regional variations. Insurance may or may not cover cryopreservation, even in fertility mandate states. Experimental procedures may not even yield viable sperm, leaving the patient's family to decide if the mere chance at future fertility options is thousands of dollars. There is debate as to whether it is ethical to recommend experimental procedures with high costs, especially without the promise of viable gametes in the future [35]. Despite these concerns, we believe that we have an ethical mandate to preserve patient and family autonomy and discuss all available options. Centers that participate in institutional review board approved protocols may require donation of a portion of the tissue towards research. This may be considered a form of coercion, especially in families who do not have resources to otherwise afford the option. While we acknowledge the injustice of the high costs of FP and unequal access, we still believe that patients and families deserve knowledge of the options so that they can fully participate in the shared decision-making process.

Innovations

Recent innovations focus on in vitro maturation including use of culture scaffolds and artificial organoids as well as identifying genetic regulators IVM. Other work, particularly in ovarian tissue and oocytes, is being done with increased harvested sample quality.

Maturation of Sperm

The current focus of FP techniques in patients with testes focuses on the utilizing spermatogonial stem cells (SSCs) to produce mature sperm, rather than relying on the harvest of already mature sperm, which are not yet present in prepubescent children. The goal of this work is to mimic the natural process of spermatogenesis. While this has been reported successful in animal models, this work has not yet translated to human pregnancy. Grady, a rhesus macaque, was the live birth product of sperm matured in vivo from grafted cryopreserved prepubertal tissue [36]. To date, this technology has not proven successful in humans. Several groups are working on various aspects of in vitro maturation. Work on growth has shown that morphological spermatozoa could be produced from SSCs when they were cultured along with Sertoli cells in a agarose-laminin hydrogel [37]. This supports the idea that Sertoli cells are critical to the spermatogenic niche and should be harvested and maintenance with the seminiferous tubules. Another study yielded elongated spermatids using a culture of agarose-embedded mouse seminiferous tubules, again highlighting the importance of multiple cell types for the maturation of sperm [38]. Maintenance of the extracellular matrix and its proteins also appears to be an important factor in maintaining the viability of sperm stem cells. Kurek et al. report that LAMA1 and type IV collagen, which are components of the testicular basement membrane, are integral to maintenance of the SSC population [39•]. With loss of these proteins the SSC population dwindles. Another group has shown that using a manufactured scaffold of gelatin and polycaprolactone may improve SSC growth [40]. If the pool of spermatogonia can be improved, the overall efficiency rate of spermiogenesis could be increased. These four studies offer several possible pathways to be explored that may allow for the development of in vitro gametogenesis. By working together, researchers will hopefully develop an efficient and reliable method of in vitro spermatogenesis.

Identifying the genetic markers of maturation may be essential for spermatogenesis. In mice, the activation of transcription factor Stra8 through nutrient depletion will initiate meiosis due to the downregulation of nutrient transporters. The consequence of Stra8 application is depletion of mature sperm [41•]. Additionally, it has been identified that human spermatogonia have upregulated oxidative phosphorylation genes, which will become downregulated once puberty begins [42]. Identification of the genetic controls of sperm maturation transition stages may be key in performing in vitro gametogenesis on SSCs. Once the mechanisms of sperm maturation are identified, protocols to mimic these processes in vitro can be developed and applied to harvested SSCs to produce mature sperm.

Maturation of Oocytes and Optimization of Harvest

The landscape of fertility preservation techniques follows similar trends to that of testicular FP advancements and focuses mainly on improving in vitro maturation of immature oocytes. This would allow for oocyte maturation and harvest from removed ovarian tissue without requiring

autotransplantation. There have been several recent innovations in the production of artificial ovaries and culture scaffolds to mimic the environment of the ovary and allow oocytes to mature in culture. In pigs, when primordial ovarian follicles were cultured with other ovarian cells in an alginate scaffold with affinity-bound bone morphogenetic protein-4 (BMP-4), the follicles matured to the preantral stage and were able to secrete estradiol at a higher level than follicles cultured without affinity bound BMP-4. Upon transplantation into mice, the cultured follicles were able to restore ovarian function [43]. Human primordial follicles have been able to transition into secondary follicles using an artificial ovary with fibrinogen and thrombin scaffolding [44•]. The scaffolding degraded over 7 days, which is a promising sign for generation of follicles that can be reimplanted back into the patient. Furthermore, 3-D printed artificial ovaries have successfully been used to culture murine oocytes up to metaphase II [45]. This research uses ovarian tumor cell lines and gelatin-methacryloyl, a protein-based hydrogel to print ovary-like cell niches for growth. When considering the use of organoid scaffolds or artificial gonads, a differentiation must be made depending on whether the organ will be transplanted into a patient or it will be maintained in vitro. Some authors posit that "the ultimate goal of an artificial ovary is re-transplantation into the human body" [44•]. For pediatric cancer patients, gonad transplantation may be desirable once they complete chemotherapy in order to re-establish full reproductive potential and reduce possible hormonal deficits. For transgender patients, autotransplantation of the ovary may not be desirable, especially if they have undergone GAHT.

Similar to the findings presented by Kurek and colleagues with spermatozoa, studies utilizing murine oocytes have shown that the preservation of extracellular matrix proteins leads to improved oocyte maturation [46]. Via the use of extracellular matrix sequestering proteins, the oocytes were able to reconstruct a supporting matrix to facilitate development. Another study showed that culturing immature oocytes with a specific growth factor mixture allowed for immature oocytes to have higher rates of cumulus cell growth, which is an essential step for oocyte maturation [47].

Another avenue of innovation is the optimization of oocyte cryopreservation. Prior to in vitro fertilization or cryopreservation, oocytes are assessed subjectively to determine their quality and, by proxy, the likelihood that they will be fit for fertilization. Oocytes are graded on visual qualities such as morphology and appearance of the cytoplasm [48, 49]. Based on large data sets and machine learning, artificial intelligence technology has been used to assess the appearance of oocytes, has been tested, and has shown to be able to predict the possibility of fertilization based on comparison with oocytes that results in a live birth [50]. Fertilization outcomes of these artificial intelligence selected oocytes have yet to be seen. Others are working on more objective quality assessment test such as the presence and quantification of oocyte competence biomarkers. Research has established that certain genes involved in oocyte processes such as nuclear maturation and extracellular matrix remodeling are expressed at different points in the oocyte's life cycle [36, 51]. Levels of these markers, such as luteinizing hormone receptor (LHR), have been used to predict outcomes of in vitro fertilization (IVF) cycles. These known biomarkers can be used to predict the maturation level of an oocyte, rather than visual cues alone. Together, these innovations seek to improve oocyte maturation and selection to improve embryo implantation and birth outcomes.

Conclusion

Advances from adult infertility over the past 70 years have made their way into the pediatric FP realm and further advanced are on the horizon. On the clinical side, we need to work together, in a multidisciplinary fashion, to ensure that these options are made available to all patients with at-risk fertility. We must also work through the ethical issues of FP with our patients, our colleagues, and our legislature. New advancements in the science of FP are essential for children and adolescents, particularly prepubertal patients with testes. Current work highlights the importance of the stem cell niche and replication of the gonadal environment for gamete maturation but further work must be done to make in vitro maturation of sperm a reality. Unfortunately, these procedures will continue to be costly in the near future but hopefully with time, there will be more equitable access to these technologies. These advancements give pediatric patients and their families more options for and certainty in preserving their fertility.

Author Contribution CV and NRM researched, wrote, and reviewed the manuscript. CV prepared the table. NRM prepared the figures.

Data Availability No datasets were generated or analyzed during the current study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Coleman E, Radix AE, Bouman WP, Brown GR, De Vries AL, Deutsch MB, Ettner R, Fraser L, Goodman M, Green J, Hancock AB, et al. Standards of care for the health of transsexual, transgender, and gender nonconforming people. World Professional Association for Transgender Health WPATH. Int J Transgend Health. 2022;23(Suppl 1):S1–259. https://doi.org/10.1080/26895269.2022.2100644. eCollection 2022.
2. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, Wallace WH, Wang ET, Loren AW. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994–2001.
3. Theroux CI, Hill KN, Olsavsky AL, Klosky JL, Yeager ND, Audino A, O'Brien SH, Quinn GP, Gerhardt CA, Nahata L. Satisfaction with fertility preservation decisions among adolescent males with cancer: a mixed methods study. Cancers. 2021. https://doi.org/10.3390/cancers13143559.
4. Vyas N, Douglas CR, Mann C, Weimer AK, Quinn MM. Access, barriers, and decisional regret in pursuit of fertility preservation among transgender and gender-diverse individuals. Fertil Steril. 2021;115:1029–1034.
5. Stein DM, Victorson DE, Choy JT, et al. Fertility preservation preferences and perspectives among adult male survivors of pediatric cancer and their parents. J Adolesc Young Adult Oncol. 2014;3:75–82.
6. Quain KM, Kyweluk MA, Sajwani A, Gruschow S, Finlayson C, Gordon EJ, Johnson EK, Persky R, Dowshen N, Chen D. Timing and delivery of fertility preservation information to transgender adolescents, young adults, and their parents. J Adolesc Health. 2021;68:619–622.
7. Yau M, Malhotra NR, Steever J, Baldisserotto E, Lin C, Fader R, Oransky M, Safer JD. Pubertal status at the time of fertility preservation in transgender girls. Endocr Pract. 2024. https://doi.org/10.1016/j.eprac.2024.01.008.
8. Wright ML, Theroux CI, Olsavsky AL, DaJusta D, McCracken KA, Hansen-Moore J, Yeager ND, Whiteside S, Audino AN, Nahata L. The impact of hiring a full-time fertility navigator on fertility-related care and fertility preservation at a pediatric institution. Pediatr Blood Cancer. 2022;69:e29857.
9. van den Berg M, Nadesapillai S, Braat DDM, Hermens RPMG, Beerendonk CCM. Fertility navigators in female oncofertility care in an academic medical center: a qualitative evaluation. Support Care Cancer. 2020;28:5733–574141.
10. Ombelet W, Van Robays J. Artificial insemination history: hurdles and milestones. Facts Views Vis Obgyn. 2015;7:137–143.
11. Miller CM, Duong S, Weaver AL, Zhao Y, Shenoy CC. Outcomes of frozen oocyte donor in vitro fertilization (IVF) cycles using fresh versus frozen sperm. Reprod Sci. 2022;29:1226–1231.
12. Peri A, Ahler A, Gook D, O'Connell MA, Bourne H, Nightingale M, Telfer M, Jayasinghe Y, Pang KC. Predicting successful sperm retrieval in transfeminine adolescents after testicular biopsy. J Assist Reprod Genet. 2021;38:2735–2743.
13. Paying for treatments. In: Alliance for Fertility Preservation. 2024. https://www.allianceforfertilitypreservation.org/paying-for-treatments/. Accessed 20 Feb 2024
14. Gat I, Toren A, Hourvitz A, Raviv G, Band G, Baum M, Lerner-Geva L, Inbar R, Madgar I. Sperm preservation by electroejaculation in adolescent cancer patients. Pediatr Blood Cancer. 2014;61:286–290.
15. Adank MC, van Dorp W, Smit M, van Casteren NJ, Laven JSE, Pieters R, van den Heuvel-Eibrink MM. Electroejaculation as a method of fertility preservation in boys diagnosed with cancer: a single-center experience and review of the literature. Fertil Steril. 2014;102:199-205.e1.
16. Schmiegelow ML, Sommer P, Carlsen E, Sønksen JO, Schmiegelow K, Müller JR. Penile vibratory stimulation and electroejaculation before anticancer therapy in two pubertal boys. J Pediatr Hematol Oncol. 1998;20:429–30.
17. Hagenäs I, Jørgensen N, Rechnitzer C, Sommer P, Holm M, Schmiegelow K, Daugaard G, Jacobsen N, Juul A. Clinical and biochemical correlates of successful semen collection for cryopreservation from 12–18-year-old patients: a single-center study of 86 adolescents. Hum Reprod. 2010;25:2031–2038.
18. Lao M, Honig SC. Evaluation of testis sperm extraction (TESE) and testis histology in the gender confirming surgery patient. American Society for Reproductive Medicine Poster Session. 2016. https://doi.org/10.1016/j.fertnstert.2016.07.395.
19. Bodri D, Guillén JJ, Polo A, Trullenque M, Esteve C, Coll O. Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles. Reprod Biomed Online. 2008;17:237–243.
20. Hassan A, Perini J, Khan A, Iyer A. Pregnancy in a transgender male: a case report and review of the literature. Case Rep Endocrinol. 2022;2022:6246867.
21. Obedin-Maliver J, Makadon HJ. Transgender men and pregnancy Obstet Med. 2016;9:4–8.
22. Light AD, Obedin-Maliver J, Sevelius JM, Kerns JL. Transgender men who experienced pregnancy after female-to-male gender transitioning. Obstet Gynecol. 2014;124:1120–1127.
23. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2019;112:1022–1033.
24. Lee S, Ryu K-J, Kim B, Kang D, Kim YY, Kim T. Comparison between slow freezing and vitrification for human ovarian tissue cryopreservation and xenotransplantation. Int J Mol Sci. 2019. https://doi.org/10.3390/ijms20133346.
25. Soares M, Saussoy P, Maskens M, Reul H, Amorim CA, Donnez J, Dolmans M-M. Eliminating malignant cells from cryopreserved ovarian tissue is possible in leukaemia patients. Br J Haematol. 2017;178:231–239.
26. Sönmezer M, Şükür YE, Saçıntı KG, Özkavukçu S, Kankaya D, Atabekoğlu CS, Cengiz Seval G, Oktay KH. Safety of ovarian cryopreservation and transplantation in patients with acute leukemia: a case series. Am J Obstet Gynecol. 2024;230:79.e1-79.e10.
27. Grellet-Grün M, Delepine B, Le Van QP, et al. A 16-year bicentric retrospective analysis of ovarian tissue cryopreservation in pediatric units: indications, results, and outcome. Front Endocrinol. 2023;14:1158405.
28. Demeestere I, Simon P, Dedeken L, Moffa F, Tsépélidis S, Brachet C, Delbaere A, Devreker F, Ferster A. Live birth after autograft of ovarian tissue cryopreserved during childhood. Hum Reprod. 2015;30:2107–2109.
29. Dolmans M-M, von Wolff M, Poirot C, Diaz-Garcia C, Cacciottola L, Boissel N, Liebenthron J, Pellicer A, Donnez J, Andersen CY. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. Fertil Steril. 2021;115:1102–1115.
30. Takae S, Iwahata Y, Sugishita Y, et al. Survey of understanding and awareness of fertility preservation in pediatric patients: is conversation about fertility preservation unpleasant for pediatric patients? Front Endocrinol. 2022;13:1074603.

31. Simana S. Creating life after death: should posthumous reproduction be legally permissible without the deceased's prior consent? J Law Biosci. 2018;5:329–354.
32. Leidig M. Russian woman may lose grandson conceived from dead son's frozen sperm. BMJ. 2006;332:627.
33. Bevers AA, Chiu L. A cadet died in tragedy. Now his parents can use his sperm to create his child, a judge rules. The Washington Post. 2019.
34. Mattingly A. Fertility preservation in patients with cancer: what the surgeon needs to know. American College of Surgeons. 2021.
35. McDougall RJ, Gillam L, Delany C, Jayasinghe Y. Ethics of fertility preservation for prepubertal children: should clinicians offer procedures where efficacy is largely unproven? J Med Ethics. 2018;44:27–31.
36. Fayomi AP, Peters K, Sukhwani M, et al. Autologous grafting of cryopreserved prepubertal rhesus testis produces sperm and offspring. Science. 2019;363:1314–1319.
37. Jabari A, Gholami K, Khadivi F, et al. In vitro complete differentiation of human spermatogonial stem cells to morphologic spermatozoa using a hybrid hydrogel of agarose and laminin. Int J Biol Macromol. 2023;235:123801.
38. Feng X, Matsumura T, Yamashita Y, et al. In vitro spermatogenesis in isolated seminiferous tubules of immature mice. PLoS ONE. 2023;18:e0283773.
39.• Kurek M, Åkesson E, Yoshihara M, et al. Spermatogonia loss correlates with LAMA 1 expression in human prepubertal testes stored for fertility preservation. Cells. 2021. https://doi.org/10.3390/cells10020241. **This study aimed to understand the importance of basement membrane protein laminin alpha 1 (LAMA1) for developing sperm stem cells. Results showed that the maintenance of LAMA1 is essential for the maintenance of a SSC population. This conclusion is important as it offers a possible mechanism for maintaining harvest cultures so that future fertility options are preserved. This study utilized prepubescent human testicular tissue, which means the conclusions drawn are directly applicable to our population of interest.**
40. Bashiri Z, Zahiri M, Allahyari H, Esmaeilzade B. Proliferation of human spermatogonial stem cells on optimized PCL/Gelatin nanofibrous scaffolds. Andrologia. 2022;54:e14380.
41.• Zhang X, Liu Y, Sosa F, Gunewardena S, Crawford PA, Zielen AC, Orwig KE, Wang N. Transcriptional metabolic reprogramming implements meiotic fate decision in mouse testicular germ cells. Cell Rep. 2023;42:112749. **The goal of this paper was to determine the genetic regulators of sperm stem cell differentiation. The study concluded that Stra8 is required for SSCs to enter meiosis. Not only does this demonstrate the importance of Stra8 for the ability of SSCs differentiation, but also highlights the detrimental effects of the protein on mature sperm. This paper is important as it details the intricacies of sperm maturation that must be understood for developing in vitro maturation techniques.**
42. Voigt AL, Dardari R, Su L, et al. Metabolic transitions define spermatogonial stem cell maturation. Hum Reprod. 2022;37:2095–2112.
43. Felder S, Masasa H, Orenbuch A, Levaot N, Shachar Goldenberg M, Cohen S. Reconstruction of the ovary microenvironment utilizing macroporous scaffold with affinity-bound growth factors. Biomaterials. 2019;205:11–22.
44.• Wang W, Pei C, Isachenko E, Zhou Y, Wang M, Rahimi G, Liu W, Mallmann P, Isachenko V. Automatic evaluation for bioengineering of human artificial ovary: a model for fertility preservation for prepubertal female patients with a malignant tumor. Int J Mol Sci. 2022. https://doi.org/10.3390/ijms232012419. **This study aimed to test the ability to culture and mature human primordial follicles in a 3D reconstructed artificial ovary with thrombin and fibrinogen. Results showed that these immature follicles have the ability to mature into secondary follicles, which is the stage at which oocytes are fully grown. Additionally, this paper specifically focuses on the ability to use this technique in prepubescent children, which is our population of interest.**
45. Wu T, Gao YY, Su J, Tang XN, Chen Q, Ma LW, Zhang JJ, Wu JM, Wang SX. Three-dimensional bioprinting of artificial ovaries by an extrusion-based method using gelatin-methacryloyl bioink. Climacteric. 2022;25:170–178.
46. Tomaszewski CE, DiLillo KM, Baker BM, Arnold KB, Shikanov A. Sequestered cell-secreted extracellular matrix proteins improve murine folliculogenesis and oocyte maturation for fertility preservation. Acta Biomater. 2021;132:313–324.
47. Amargant F, Zhou LT, Yuan Y, et al. FGF2, LIF, and IGF1 (FLI) supplementation during human in vitro maturation enhances markers of gamete competence. Hum Reprod. 2023;38:1938–1951.
48. Lazzaroni-Tealdi E, Barad DH, Albertini DF, Yu Y, Kushnir VA, Russell H, Wu Y-G, Gleicher N. Oocyte scoring enhances embryo-scoring in predicting pregnancy chances with IVF where it counts Most. PLoS ONE. 2015;10:e0143632.
49. Lemseffer Y, Terret M-E, Campillo C, Labrune E. Methods for assessing oocyte quality: a review of literature. Biomedicines. 2022. https://doi.org/10.3390/biomedicines10092184.
50. Peschansky C, Patel S, Amir J, et al. Picture perfect?: determining the clinical utilization of artificial intelligence in oocyte cryopreservation. Fertil Steril. 2021;116:e157.
51. Sirait B, Wiweko B, Jusuf AA, Iftitah D, Muharam R. Oocyte competence biomarkers associated with oocyte maturation: a review. Front Cell Dev Biol. 2021;9:710292.