Fertility Preservation for Pediatric Patients: Current State and Future Possibilities

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Abbreviations and Acronyms

ART = assisted reproductive technology

BMT = bone marrow transplantation

CED = cyclophosphamide equivalent dose

DSD = disorder/difference of sex development

eIVFG = encapsulated in vitro follicle growth

FP = fertility preservation

GnRHa = gonadotropin releasing hormone agonists

OTC = ovarian tissue cryopreservation

SSC = spermatogonial stem cell

TESE = testicular sperm extraction

Purpose: This review provides an overview of pediatric fertility preservation. Topics covered include the patient populations who could benefit, the current state of fertility preservation options and research, and considerations related to ethics and program development.

Materials and Methods: A broad Embase® and PubMed® search was performed to identify publications discussing investigational, clinical, ethical and health care delivery issues related to pediatric fertility preservation. Relevant publications were reviewed and summarized.

Results: Populations who could benefit from fertility preservation in childhood/adolescence include oncology patients, patients with nononcologic conditions requiring gonadotoxic chemotherapy, patients with differences/disorders of sex development and transgender individuals. Peripubertal and postpubertal fertility preservation options are well established and include cryopreservation of oocytes, embryos or sperm. Prepubertal fertility preservation is experimental. Multiple lines of active research aim to develop technologies that will enable immature eggs and sperm to be matured and used to produce a biological child in the future. Ethical challenges include the need for parental proxy decision making and the fact that fertility preservation procedures can be considered not medically necessary. Successful multidisciplinary fertility preservation care teams emphasize partnerships with adult colleagues, prioritize timely consultations and use standardized referral processes. Some aspects of fertility preservation are not covered by insurance and out-of-pocket costs can be prohibitive.

Conclusions: Pediatric fertility preservation is an emerging, evolving field. Fertility preservation options for prepubertal patients with fertility altering conditions such as cancer and differences/disorders of sex development are currently limited. However, multiple lines of active research hold promise for the

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future. Key considerations include establishing a multidisciplinary team to provide pediatric fertility preservation services, an appreciation for relevant ethical issues and cost.

Key Words: testis, ovary, pediatrics, fertility preservation, disorders of sex development

THE field of pediatric FP is rapidly evolving. Available technologies for 1) preservation of reproductive tissue and cells, and 2) maturation and use of these tissues and cells for future reproduction are ever expanding. Researchers and clinicians have begun to apply these technologies to multiple populations.

Many pediatric patients are at risk for future infertility due to medical conditions and treatments. As the most well-known example, many oncology patients are at risk for future infertility. Patients with nonmalignant disorders treated with immunosuppression or stem cell transplant can also face fertility challenges. Finally, individuals with gender and sex diversity, including those with DSD and those who are transgender, may have reduced fertility potential. Adult survivors of pediatric cancers,[1,2] individuals with DSD[3] and those who are transgender[4] all express concern about not addressing issues related to future fertility in childhood. Available information also indicates that families desire information regarding FP even when children are only eligible for experimental options.[5]

Most urologists are involved in the treatment of oncology patients and many also care for gender and sex diverse individuals. Urologists also provide FP consultations and perform the relevant surgical procedures for male patients. When considering pediatric FP, it is important to understand the populations of patients who may face fertility challenges, the future expectations regarding applicable ART and the range of ethical, practical and financial issues that may arise. This review provides an overview of 1) fertility related issues facing children who are undergoing gonadotoxic therapies and those with gender and sex diversity, 2) current and future options for pediatric FP, 3) ethics related to pediatric FP, 4) issues to consider when building a pediatric FP program and 5) financial considerations.

MATERIALS AND METHODS

We performed broad Embase® and PubMed® searches for pediatric fertility preservation, fertility preservation and child, fertility preservation and adolescent, and the MeSH® headings pediatric AND fertility. Article titles and abstracts were reviewed to identify publications discussing the range of investigational, clinical, ethical and health care delivery issues related to pediatric FP. Non-English language articles, abstracts, book chapters and editorials were excluded and only used to identify primary sources. Review articles and case reports were used to identify primary sources and were included in this review when they raised key issues not explicitly discussed in the primary literature.

The initial search generated 109 primary articles published between January 2006 and March 2016. Additional articles were identified for inclusion by reviewing the initial articles identified. All relevant publications were then categorized by subtopic and selected for inclusion based on relevance to the scope of this review.

RESULTS

Patient Populations with Future Fertility Concerns

Oncology Patients. Cancer treatments commonly affect the fertility potential of pediatric patients as adults. Men who are childhood cancer survivors are half as likely to achieve a pregnancy compared to their siblings.[6,7] Rates of infertility in female survivors of childhood cancers vary in the literature, ranging from 16% to 41%.[8,9] Fertility effects of gonadotoxic treatments depend on patient related factors, including age and gender, and treatment related factors, including type and cumulative dose of chemotherapy, dose and site of radiation, and type of surgery performed.

Alkylating agents are particularly notable for gonadotoxicity. Most contemporary treatment regimens may include more than 1 alkylating agent. Thus, the summed alkylating agent dose score and CED have been used to assess alkylating agent exposure and risk of gonadotoxicity.[10] Summed alkylating agent dose scores range from 0 to 12.[11] CED ranges from 0 to 20,000 mg/m^2 or greater[10] with higher scores indicating increasing exposure to alkylating agents, conferring a higher risk of infertility. CED is currently the most commonly used measure of alkylating agent exposure. CED score ranges greater than 7,500 mg/m^2 are associated with the highest risk of infertility.[10] CED negatively correlates with sperm concentration in adult male long-term childhood cancer survivors,[12] although there is substantial overlap of CED with normospermia, oligospermia and azoospermia. Increasing CED scores are associated with a higher likelihood of nonsurgical premature menopause among female survivors of childhood cancers.[10]

Boys receiving high doses of cyclophosphamide or procarbazine[6,13–15] are at particularly high risk for permanent azoospermia. Other alkylating agents, including ifosfamide and cisplatin, have also often

been associated with oligospermia/azoospermia. In males younger age or prepubertal state is not thought to be gonadoprotective.[6,14] In girls risk factors for infertility include age with those of or approaching reproductive age at the time of cancer treatment at higher risk, the cumulative dose of alkylating agents, particularly cyclophosphamide, lomustine and procarbazine, and a diagnosis of Hodgkin's lymphoma.[16,17]

Among nonalkylating chemotherapeutic agents bleomycin has had inconsistent findings regarding gonadotoxicity. Exposure to bleomycin was found to be a risk factor for infertility in a small group of cancer survivors,[7] although this was not demonstrated in other studies.[18] Actinomycin, vinblastine and vincristine appear not to have deleterious effects on spermatogenesis.[14] Little is known about the gonadotoxicity of newer agents.

In boys radiation can cause infertility because the testicular germinal epithelium is particularly sensitive to its gonadotoxic effects. Testicular radiation doses as low as 0.1 to 1.2 Gy can damage dividing spermatogonia and disrupt cell morphology, resulting in oligospermia or azoospermia. Leydig cells are more resistant to damage from radiation. Because of this, male survivors frequently progress through puberty normally and have normal potency despite severe impairment of spermatogenesis. However, higher doses of testicular radiation (greater than 20 Gy in prepubertal males and greater than 30 Gy in sexually mature males) can result in Leydig cell dysfunction.[19,20]

Direct or scatter radiation to the female reproductive organs, such as total body irradiation, and spinal, abdominal and/or pelvic radiation, may damage the female reproductive organs. Higher doses of radiation to the ovaries, especially greater than 10 Gy, increase the likelihood of acute ovarian failure or nonsurgical premature menopause.[17] Ovarian/uterine radiation doses greater than 5 Gy decrease the likelihood of ever being pregnant.[8,16]

Cranial (hypothalamic/pituitary) radiation or central nervous system neoplasms can cause central hypogonadism, which can impair germ cell function in both genders. As an example, hypothalamic/pituitary radiation doses of 30 Gy or greater decrease the chance of pregnancy in female survivors of childhood cancer.[16] In general the effects of hypogonadism associated with cranial radiation alone can be treated with hormonal supplementation such that FP is not required. However, many patients who undergo cranial radiation are treated concurrently with gonadotoxic therapies such that FP may be advised.

Effects of Surgery. Patients who require bilateral gonadectomy or gonadectomy of a solitary gonad for cancer treatment will be rendered infertile. Women who have undergone oophorectomy but not hysterectomy may choose to attempt pregnancy via an egg donor. Men who have undergone retroperitoneal lymph node dissection or extirpative pelvic surgery may have erectile or ejaculatory dysfunction due to nerve damage or direct injury to the ejaculatory pathway. They may require ART if they desire biological children.

Nononcology Patients with Future Fertility Concerns

Other Patients Receiving Immunosuppression. Patients with nonmalignant rheumatological and hematological conditions, and those undergoing solid organ transplantation also face potential infertility when the conditions require gonadotoxic immunosuppressive treatments. Treatments such as stem cell transplantation, alkylating agents and other immunosuppressive therapies place these patient populations at risk. For instance, a study of 44 patients with sickle cell anemia demonstrated oligospermia in all who were treated with hydroxyurea, a nonalkylating DNA synthesis inhibitor.[21] Sperm counts did not fully recover after hydroxyurea discontinuation. As another example, sirolimus, a mammalian target of rapamycin inhibitor, has been associated with infertility in male and female patients who undergo renal transplantation.[22] The effects appear to be reversible with resumption of normospermia and menstrual cycling upon discontinuation.

Patients with Gender and Sex Diversity: Differences/Disorders of Sex Development and Transgender Patients with Gender Dysphoria. DSD (also known as intersex) conditions occur when there is incongruence among the chromosomal, gonadal or phenotypic sex of an individual.[23] Unlike patients with cancer, who have normal inherent fertility potential, most patients with DSD have inherently abnormal fertility potential. The 4 main risks to future biological fertility in DSD cases are 1) abnormal gonadal development, 2) gonadectomy performed for the risk of malignancy, 3) abnormal hormone production and 4) potential discordance between gonadal type and gender identity. Appendix 1 presents these risks in more detail.

Fertility potential has been documented in some DSD conditions, including Klinefelter syndrome,[24] Turner syndrome[25] and ovotesticular DSD.[26] However, the scarcity of data on most conditions and heterogeneity between and in DSD conditions hinder our knowledge of fertility potential and, thus, the ability to counsel patients accurately. Nevertheless, many patients with DSD face early gonadal failure and/or gonadectomy, and so may

benefit from some of the FP options discussed in this review.

Transgender (trans) individuals include those who identify with a gender other than the birth assigned sex. Gender dysphoria is the DSM-5® (Diagnostic and Statistical Manual of Mental Disorders) diagnosis used to describe psychological distress associated with being transgender. Medical treatments in transgender children and adolescents with gender dysphoria may impact future fertility. Pubertal suppression with GnRHa is used starting as early as Tanner stage 2. This is a reversible treatment used to prevent the development of permanent secondary sex characteristics and alleviate the psychological distress associated with these changes.[27] However, GnRHa administration also pauses gonadal maturation.[28]

Many transgender adolescents elect to initiate gender affirming hormones (eg testosterone in a transman) concurrently with GnRHa such that germ cells never fully mature.[27] The administration of gender affirming hormones may also negatively impact gonadal function and to our knowledge the long-term fertility effects are unknown. Thus, a discussion of FP options should occur prior to beginning any hormonal therapy for gender dysphoria.[29]

Although it is still an emerging concept, there is precedent in the literature for preserving biological fertility in transgender adolescents. ASRM (American Society for Reproductive Medicine) recommends that transgender individuals should be provided with equal access to fertility services.[30] Transgender young people have successfully preserved fertility prior to physical transition. As an example, a 17-year-old transgender man successfully underwent oocyte cryopreservation before initiating gender affirming hormonal therapy.[31]

Preservation of Native Gonadal Tissue during Treatment

Radiation. Strategies to decrease ovarian radiation exposure include oophoropexy (surgical repositioning of the ovaries away from the radiation field) and gonadal shielding. A recent report indicates the possibility of spontaneous fertility in women who have received total body irradiation with gonadal shielding.[32] Gonadal shielding can also help reduce testicular radiation exposure. A study of 30 adult survivors of BMT for a variety of conditions indicated that those who received radiation without gonadal shielding had smaller testis volume than those who underwent BMT with radiation and gonadal shielding or BMT with no radiation.[33] However, spontaneous fertility was only present in 1 of the 9 patients (11%) who underwent radiation with gonadal shielding and in none of the other patient groups.[33] This indicates that testicular shielding alone does not fully protect fertility in these patients undergoing multimodal therapy.

Chemotherapy. Continuous GnRHa therapy is an experimental FP option for peripubertal or postpubertal female patients who are receiving chemotherapy. The aim is to protect ovarian function by simulating a prepubertal hormonal environment. Initial studies in patients with breast cancer have shown promising but not definitive fertility outcomes.[34] Blumenfeld et al recently reported increased odds of spontaneous conception in young women with a variety of oncologic diagnoses who underwent GnRHa administration with chemotherapy compared with those treated with chemotherapy alone.[35] Adolescents as young as 14 years were included in this nonrandomized retrospective study. GnRHa and other attempts at hormonal protection in young men have not been consistently successful. Thus, there is currently little impetus to adopt this strategy in peripubertal and postpubertal adolescent males.

Pretreatment Pediatric Fertility Preservation Options and Future Directions

Female. Peripubertal or postpubertal girls facing fertility altering conditions or medical treatments can undergo FP via ovarian stimulation with oocyte retrieval and cryopreservation, analogous to the initial phase of an in vitro fertilization cycle. Oocyte retrieval and cryopreservation may be an undesirable option in some patients due to potential side effects of the hormonal interventions or concerns about delaying cancer treatment.[36] As a time efficient option that does not require hormonal stimulation, adolescents with a high likelihood of future infertility are also eligible for OTC.

In prepubertal girls experimental OTC is the only pretreatment option to preserve future fertility potential.[37] Availability is currently limited to a few academic institutions. Ovaries from pediatric patients contain large numbers of follicles with enclosed oocytes. In prepubertal children most of these oocytes are immature and so are not yet capable of reproduction. Ovarian tissue biopsy or unilateral oophorectomy procedures preserve these primary oocytes through tissue cryopreservation in cases in which medical treatments are likely to result in infertility.[38] Bilateral oophorectomy is never performed for FP in case the patient retains some ovarian function after gonadotoxic therapy. Retaining at least 1 ovary provides the potential for spontaneous transition through puberty and limited endocrine cyclicity prior to premature menopause.

Technologies of storage and in vitro maturation of cryopreserved ovarian tissues are still under

development. Thus, OTC is considered experimental in patients of all ages at this juncture. The 2 main ways that the preserved tissue may be used are 1) ovarian tissue transplantation or 2) in vitro ovarian follicle growth and oocyte maturation.

Tissues from pediatric patients that are cryopreserved can be transplanted back to the patient. Such transplants have resulted in restoration of puberty,[39] suggesting that current cryopreservation methods result in retained ovarian function. Moreover, more than 60 cases of human live birth after tissue transplantation have been reported in adult cancer survivors.[40] Traditionally, slow freezing protocols have been used for OTC. These protocols were used in the reported cases of live births after ovarian tissue transplantation.[40] Recent investigations have aimed to improve cryopreservation methods by optimizing vitrification protocols with the goal of maintaining oocyte viability and function similar to fresh tissue.[41]

In patients with hematological malignancies a concern regarding ovarian transplants is reintroduction of the prior malignancy.[42,43] This is also a potential concern in patients with Ewing sarcoma.[44] Follicular function appears to be retained through surgical removal and cryopreservation. New options for the maturation of ovarian tissue while also mitigating cancer transplant risk are still being developed. A method to decrease the risk that the transplant will reintroduce cancer includes transplanting ovarian follicles rather than the entire ovary, which may harbor cancer cells.

One current line of research involves isolating ovarian follicular tissue, which is then grown using biomaterials that provide artificial support. The most applied biomaterial is a hydrogel called alginate and the method is described as eIVFG. Live mouse offspring have been born from eggs matured after eIVFG and human metaphase II eggs have been created.[45] While fertilization is not possible in human eggs under research protocols, embryos have been created from eIVFG rhesus monkey follicles.[46] Work is ongoing to improve the efficiency and the quality of the methods.

Current animal studies are also examining the use of artificial ovaries that could replace destroyed tissue.[47] These gonadal prostheses could use decellularized tissue constructs or 3-dimensional printed tissues that are recellularized with native cells. Long-term goals include a scenario in which somatic and germ cells derived from the patient induced pluripotent stem cells would populate these artificial constructs and provide endocrine and fertility to pediatric cancer survivors. This line of work is currently limited to the rodent model and has yet to be translated to humans or other primates. Importantly girls facing fertility altering medical conditions and treatments have time for this ongoing research to mature.[48]

Male. In peripubertal or postpubertal adolescent males FP can be achieved through cryopreservation of an ejaculated semen sample. Feasibility of this approach has been demonstrated in individuals as young as 13 years.[49] When this is not possible due to patient age, anatomy, concerns about psychological impact or azoospermia, which is common among male patients with cancer, sperm can often be surgically retrieved from the testicle via various TESE procedures.

Approximately 50% of males with azoospermia prior to the initiation of cancer treatment will have sperm present in the testicular tissue at the time of attempted sperm extraction and this procedure has been dubbed oncoTESE.[50] Peripubertal or postpubertal adolescents who are unable to provide an ejaculated specimen may also be candidates for electroejaculation.[51] Sperm obtained via ejaculated semen samples or TESE procedures can be cryopreserved and then used during future ART procedures.

Fertility preservation in prepubertal boys is currently experimental. Given that these patients have not yet entered puberty, they do not yet produce sperm and no mature gametes are available for cryopreservation. Similar to ovarian tissue, prepubertal testicular tissue cryopreservation is currently performed via slow freezing techniques, which have been demonstrated to maintain testicular integrity after thawing.[52] Also similar to preservation of ovarian tissue, vitrification protocols have shown promise as an alternative strategy to preserve prepubertal testicular tissue.[53] Current investigational protocols rely on the hope that future technologies, such as the stem cell based technologies described, will someday emerge as a successful means of using experimentally cryopreserved immature testicular tissue.

In 1994 SSC transplantation was first described in an animal model.[54] Brinster and Zimmermann reported the introduction of a testicular tissue suspension into infertile recipient mice with the successful observation of active spermatogenesis in these recipients several months later and with the resultant birth of offspring mice.[54] This initial work gave rise to homologous SSC transplantation in other species, including rats, sheep and monkeys. Cryopreservation and later transplantation of SSCs is a promising approach because these cells have been shown to remain functional even after a cycle of cryopreservation and subsequent thawing. Autologous grafting and xenografting of intact testicular tissue are also experimental approaches to generate sperm. These methods have been successfully used in animal models to

fertilize partner oocytes by intracytoplasmic sperm injection.[55]

SSC culture is another investigative approach currently under study. After testicular biopsy in the prepubertal boy SSCs are isolated from the excised testicular tissue. The goal is for these SSCs to then be established and expanded in long-term cultures while maintaining the potential to effectively proceed through the process of spermatogenesis. Groups at a number of centers have reported successful establishment and maintenance of SSC cultures.[56,57] However, at this time no methodology has been reported and independently reproduced by another group.

Another technique under study for FP in prepubertal males involves the introduction of a suspension of SSCs and other essential testicular cell types into decellularized testicles in an effort to achieve de novo morphogenesis of the testicle.[58] Propelling this work are prior studies demonstrating complete spermatogenesis with mouse SSC co-incubation with mouse or rat testicular cells in an immune deficient mouse model. Theoretically, to expand this to human application patient SSCs could be incubated with a testicular tissue suspension from a donor with the aim of establishing an environment in which spermatogenesis can progress to completion.

Ethics of Pediatric Fertility Preservation

In pediatric patients facing a medical diagnosis or treatment that presents a risk of infertility the FP options vary by diagnosis, patient age and sex, and family beliefs among many other factors. Thus, the situation of each child presents unique ethical challenges. Given this complexity, a full ethical discussion is beyond the scope of this review. It was covered comprehensively in ethical analyses such as those by Di Pietro et al.[59,60] However, the key biomedical ethical principles of beneficence, nonmaleficence, justice and autonomy can inform counseling and decision making regarding FP in pediatric patients. Appendix 2 outlines these key issues, including how each principle provides support for and argues against pediatric FP.

In addition to the general ethical issues presented in Appendix 2, an issue relatively unique to the oncology population is the urgency with which oncologic treatments must start. Timing of potential FP must be balanced with the initiation of potentially lifesaving therapies and FP counseling occurs during a time of extreme family stress. Moreover, it is imperative to discuss the expectation that stored tissue should be disposed of in the event that the patient does not survive.[60]

Counseling regarding FP in patients with DSD is generally less urgent than in oncology patients but it is often done in the context of great uncertainty regarding the inherent fertility potential of the patient. Also, for certain DSD conditions gender identity does not necessarily match gonadal type (ie women with complete androgen insensitivity have sperm in the gonads). In transgender adolescents body dysphoria is common, making the procedures to obtain reproductive tissue potentially distressing to the patient and a possible barrier to pursuing FP.

Building Pediatric Fertility Preservation Program: Recommendations and Challenges

Although pediatric FP is a relatively new field, groups at multiple institutions have published their experiences with building FP programs that serve pediatric patients.[5,38,61,62] The supplementary Appendix (http://jurology.com/) outlines concepts gleaned from experiences at centers building multidisciplinary FP care teams. Key points include 1) outlining consistent FP information that will be conveyed to every family, including clarity about which procedures are considered experimental, 2) ensuring rapid access to the FP team, given the urgency inherent in providing oncologic care, 3) determining criteria for patient assent and 4) establishing standardized referral processes, which increased the rate of sperm banking when implemented at Seattle Children's Hospital.[63]

Research has identified multiple barriers to providing FP services, including provider bias, time constraints, concerns regarding cost and lack of partnership with adult reproductive specialists.[64] As an example of provider bias, a recent investigation of patients, parents and oncology providers indicated discordance between family desire and provider willingness to offer testicular cryopreservation.[65] In that study by Gupta et al providers were less willing to offer FP to families of perceived lower socioeconomic status or those who did not receive care at an institution that offered testicular cryopreservation.[65]

Health care providers also lack knowledge about FP options, limiting the ability to educate patients and families. Despite the ASCO (American Society of Clinical Oncology) clinical recommendations that all oncology patients receive information on FP and the APHON (Association of Pediatric Hematology/Oncology Nurses) White Paper endorsing FP as a patient right, the majority of pediatric oncology care providers have reported that they have not received education or training on the topic of FP.[66,67]

Financial Considerations

The financial cost of FP in pediatric patients can be substantial. Exact costs vary by hospital and insurance coverage of the components of FP also vary. Although some states (eg Illinois) mandate coverage of infertility services by law, pediatric patients

generally do not meet the strict definition of infertility (ie attempting to conceive for greater than 1 year). Thus, families must pay for many FP services out-of-pocket. There are up-front costs at the time of fertility preservation but families should also be informed of the future costs of reproductive medicine services when pregnancy is attempted.

Surgical tissue retrieval procedures may be covered by insurance and some hospitals have dedicated philanthropic funds for families who do not have coverage for these services. When possible, surgical procedures are also bundled with other necessary procedures to minimize anesthetic exposure and cost. Oocyte cryopreservation and sperm banking, and yearly storage costs for any type of reproductive tissue or cells are often not covered by insurance. These recurring costs can be prohibitive for many families, particularly in the context of a new cancer diagnosis, when financial hardship is common.[68] A recent study from Quebec demonstrated that providing coverage for ART increased the number of sperm banking visits among patients with cancer, suggesting that improving coverage may increase access to and use of FP services.[69]

Summary and Conclusions

Until recently infertility was not considered a potential problem (ie due to lack of knowledge) or it was assumed to be an unavoidable consequence of pediatric cancer treatments. Developments in FP and ART have now made it possible for more survivors of pediatric cancers to have biological offspring. Pediatric FP technologies are also expanding to other populations, including nononcologic conditions requiring gonadotoxic therapies and individuals with gender and sex diversity. Current challenges include uncertainty about future ART, cost and multiple ethical considerations. However, capabilities are expanding such that current and future generations of young people affected by fertility altering conditions will potentially have far more options for FP than currently exist today.

APPENDIX 1

Fertility Effects in Differences/Disorders of Sex Development

Reason for Infertility	Details	Implications for Fertility Preservation
Abnormal gonadal development	Abnormal gonadal development (eg streak gonads, dysgenetic gonads) results in progressive, early gonadal failure.	Presence and quality of germ cells in these abnormal gonads is largely unknown. Early gonadal failure may necessitate prepubertal FP if future biological fertility is desired.
Risk of malignancy	Gonadectomy may be performed due to risk or presence of neoplasm.	Early gonadectomy may necessitate prepubertal FP if future biological fertility is desired.
Abnormal hormone production	Abnormal hormone production or responsiveness may lead to impairment in sperm or oocyte production.	Decreased number/quality of reproductive cells may necessitate FP.
Germ cell type incongruent with gender identity	Gonads and germ cells may not match the patient's gender identity. This has led to a past assumption of infertility, despite the presence of potentially viable reproductive material.	FP and assisted reproduction may be necessary for biological parenthood.

APPENDIX 2

Ethical Considerations in Pediatric Fertility Preservation

Ethical Principle	Fertility Preservation—Pro	Fertility Preservation—Con
Beneficence (Benefit to the patient and society)	Childhood FP may be the only chance to preserve the possibility of biological parenthood Potential for hormone restoration Societal benefit from research	FP procedures can be considered "not medically necessary" Patient may not benefit from research
Nonmaleficence (First do no harm)	FP could prevent distress associated with future infertility	Surgical FP procedures carry small risk of complications FP procedures could delay medically necessary treatments such as chemotherapy FP procedures may be physically or psychologically distressing to some patients
Justice (Equity in health care)	FP should be offered to all eligible patients FP options should be discussed with best available information about risks, benefits and outcomes	Cost (and lack of insurance coverage for some costs) can prevent equal access for all eligible patients Allocation of resources and health care dollars; not all patients have access to FP providers
Respect for autonomy (Individuals make decisions for themselves)	FP provides options for the future about how to build a family Preservation of full reproductive potential has been identified as a priority for previous survivors of childhood cancers[1,2]	Pediatric FP requires proxy decision making Patient wishes may be at odds with parental wishes—how to proceed? Parents do not agree how to proceed Use of tissue for research purposes in minor patient Questions about what to do with tissue if the child does not survive

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EDITORIAL COMMENT

The field of fertility preservation is gaining a lot of attention. It is likely to continue to expand thanks to the speed of technological advances and increasing awareness of factors that can threaten the future reproductive ability of children and adolescents. The current state of affairs, promising new frontiers and ongoing controversies, is well summarized in this article by Johnson et al.

Two important themes deserve to be highlighted. First is the importance of a multidisciplinary approach involving a diverse, complementary group of specialists. When pushing the research and clinical agenda forward, the involvement of ethicists, policy makers, representatives from funding sources, patients and families is critical. Second is the desire and importance to build capacity and expand services to centers with the volume and interest to target these vulnerable patient populations. It is a daunting task to get a program up and running and we should encourage and support each other. A strong conceptual basis and a roadmap along with lessons learned from implementation at established centers are vital information for those interested in joining the fertility preservation movement.

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