Review Article

Fertility counseling and preservation: considerations for the pediatric endocrinologist

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Abstract: Infertility is a distressing consequence of numerous pediatric medical conditions and treatments. The field of pediatric fertility preservation has expanded rapidly over the past decade, and clinical guidelines emphasize the importance of discussing infertility risk and fertility preservation options with patients and families in a timely manner. Understanding the various mechanisms and presentations of fertility issues across diagnoses is imperative to provide counseling to patients and families, and identify individuals who may benefit from fertility preservation. The goals of this manuscript are to outline current fertility preservation options in pediatrics, review populations at-risk for infertility that are seen in pediatric endocrinology, and discuss other important issues related to fertility preservation including ethical considerations.

Keywords: Infertility; fertility preservation

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Introduction

Infertility is known to diminish quality of life, and cause distress among individuals and couples trying to conceive (1). While this is an issue that may not immediately appear to be relevant in pediatrics, there are many childhood conditions and treatments which pose a risk to future fertility. Guidelines have thus been published by groups such as the American Academy of Pediatrics encouraging providers to discuss infertility risk and fertility preservation options in a timely manner (2). Of note, a significant number of these children will be seen by a pediatric endocrinologist at some point during their medical journey, for management of hypogonadism and/or other endocrine sequelae of various treatments.

The majority of research with regard to fertility in the pediatric setting has been conducted in oncology. In the past 5–10 years, however, it is becoming increasingly apparent that there are several groups of patients in which fertility counseling would be beneficial, including patients with differences of sex development, congenital causes of primary gonadal failure, gender dysphoria, and others. Fertility counseling and provider comfort in discussing topics such as sperm cryopreservation have been shown to impact fertility preservation rates among adolescents (3). Unfortunately, fertility related practices in pediatrics remain inconsistent at this time due to a variety of factors, such as time constraints, inadequate access to fertility specialists, and insufficient knowledge of infertility risk and fertility preservation options.

In a national survey of 284 endocrinologists, only 36% reported feeling that their training in fertility was adequate, and 75% wanted more guidance in this area (4). An awareness of and knowledge about these issues would help pediatric endocrinologists appropriately counsel their patients as well as connect them with the resources

that may protect or preserve parenthood options for the future. In this context, the goals of this manuscript are to (I) outline current fertility preservation options in pediatrics; (II) review pediatric populations at-risk for infertility that are seen in pediatric endocrinology; and (III) discuss other important issues related to fertility preservation including ethical considerations.

Overview of fertility preservation options

Fertility preservation options for females

Established fertility preservation options for females include ovarian transposition/shielding, oocyte cryopreservation, and embryo cryopreservation. When these methods are not feasible or relevant due to factors such as clinical situation, age/pubertal stage, time constraints, and financial considerations, other options such as medications or ovarian tissue cryopreservation (OTC) may be offered. All of these options should ideally be considered before gonadotoxic therapy and/or prior to further decline in gonadal function.

Ovarian transposition/shielding

In cases where the main cause of ovarian damage is pelvic radiation, using a shield, or surgically removing the ovaries outside of the radiation field (and affixing to a site such as the uterosacral ligament), may decrease the risk of infertility (5). It is important to note that some radiation exposure may still occur due to scatter.

Oocyte cryopreservation

Oocyte and embryo cryopreservation are established, or "standard of care", fertility preservation options available to females who have experienced menarche. Both options require a patient to undergo hormonal stimulation followed by transvaginal retrieval of oocytes; this entire process takes approximately 2 weeks (6). Since embryo cryopreservation requires a sperm donor, the change in status of oocyte cryopreservation from "experimental" to "established" in 2013 was of great benefit to pediatric populations (7). Preserving oocytes preferentially conserves family planning autonomy should the relationship status be different by the time pregnancy is desired.

Unfortunately, barriers persist, precluding widespread use of this technology: (I) invasiveness of the procedure may be less desirable or poorly tolerated among adolescents; (II) hormonal stimulation may pose risk in some medical conditions; (III) taking 2 weeks to complete the process may not be feasible in situations where treatment is medically urgent; and (IV) high cost with low rates of insurance coverage limits accessibility to many individuals. Attempts should be made to mitigate these barriers. Establishing a relationship with a fertility specialist/reproductive endocrinologist who has expertise in these procedures, can schedule urgent appointments, and is sensitive to the needs of adolescents is crucial.

OTC

In prepubertal females, the only option at this time is OTC. This is a surgical procedure by which part of or a whole ovary is removed and cryopreserved. This tissue may later be implanted orthotopically (at the site of the ovaries) or heterotopically, in locations such as the abdomen or even at a distant site like the forearm (8). In either case, live births have only been reported with autotransplantation of tissue; thus, caution must be used in certain populations. For instance, in individuals with hematologic malignancies, there is a possibility of reintroducing malignant cells into the patient. OTC may also be suboptimal in other groups where eventual hormonal stimulation would be unsafe or undesirable (such as transgender individuals). Research on *in vitro* maturation is ongoing (9). Additionally, studies are ongoing to examine slow-freezing versus vitrification in OTC procedures (10).

There have been greater than 80 babies born to women who have undergone OTC (11). It should be noted, however, that this technique continues to straddle the barrier between experimental (in the United States) and standard of care (in other countries such as Europe). Particular attention should be given to the use of OTC in the youngest patients as there is a paucity of data in this area. The first live birth from a woman who underwent OTC in a pre-pubertal state (at the age of 9 years) was published in December 2016 (12). Questions remain about the ability of cryopreserved tissue to be re-implanted and undergo normal follicular development in even younger patients. This has been evaluated using human ovarian tissue from pre-pubertal girls, which was implanted in mice and stimulated with gonadotropin; a high rate of follicles survived this experiment and follicular development was noted after stimulation, which is promising (13). While outcomes are difficult to predict in this age group, this remains the only option for fertility preservation, thus this information ought to be shared with families during fertility counseling.

Medications

If treatment must start quickly or a patient is unable or unwilling to undergo more invasive procedures, hormonal gonadal suppression can be used. This is typically accomplished with a gonadotropin releasing hormone (GnRH) agonist, such as leuprolide, which ultimately results in decreased LH and FSH and suppression of ovarian function. This is a non-invasive option for preservation that can be utilized during the treatment period and stopped once therapy is complete. While some studies have shown promise, others have not shown a significant benefit with regard to pregnancy and live birth rates (14,15). Thus, this is not considered an established fertility preservation option at this time.

Fertility preservation options for males

Gonadal shielding and sperm cryopreservation are established fertility preservation options for males, while testicular tissue cryopreservation (TTC) remains experimental. To maximize benefit, these options should be pursued prior to gonadotoxic therapy. Additionally, while age-related decline of gonadal function is less clearly defined in males compared to females, there are some studies suggesting a decline in testosterone and sperm production over time in healthy males, as well as progression of oligospermia to azoospermia in males exposed to gonadotoxic agents (16-18). The "optimal" age for fertility preservation has been identified for certain populations, discussed further in the next section.

Gonadal shielding

As described above for females, shielding should be considered in males to mitigate effects testicular radiation. Doses as low as 0.1 Gy can damage spermatogonia and doses exceeding 4–6 Gy often lead to permanent azoospermia (19,20).

Sperm cryopreservation

In pubertal males, the gold standard method of fertility preservation is sperm cryopreservation (3). A sample is collected via masturbation, and a local facility needs to be identified when the sample can be analyzed and stored for future conception via *in-vitro* fertilization/intracytoplasmic sperm injection. In males who are unable to produce a sample secondary to acute illness, age/maturity level, anatomic considerations, or personal/religious beliefs about masturbation, sperm can be extracted through alternate means. Surgical options include testicular sperm extraction (TESE), or micro-dissection testicular sperm extraction (micro-TESE), which is the preferred method in patients who have impaired sperm production due to their underlying condition or prior treatment. Electroejaculation (EEJ) is another option (also performed under general anesthesia) where a rectal probe is used to deliver an electrical current to trigger ejaculation (21). Sperm retrieval has been reported using these approaches in males as young as 12 years of age and with 6 mL testes (22).

TTC

In prepubertal males, only experimental options exist for fertility preservation. TTC research protocols are open at several centers across the United States. The concept is similar to that of OTC, in which part of the testicle is removed and frozen. However, there have been no reports of re-implantation of the testicular tissue resulting in human live births as of yet. Several animal models have resulted in live births after spermatogonial stem cells were reimplanted in seminiferous tubules, and further research is in process, with the hope that this technology will be further developed in the near future (23,24).

Pediatric populations at risk for infertility

Many medical conditions and therapies have the potential to affect fertility. Populations that are most commonly encountered by pediatric endocrinologists are described below. It is also important to note that any patient referred to a pediatric endocrinologist due to concerns for delayed puberty or amenorrhea could also be at risk for fertility impairment, since the hypothalamic-pituitary-gonadal axis ultimately controls both hormone production (testosterone and estrogen) and gamete production (sperm and eggs).

Treatment induced infertility

Oncologic therapy

Currently the largest volume of literature about treatment induced infertility exists in oncology. Recent data from the Childhood Cancer Survivor Study show that both male and female survivors have significantly higher rates of fertility problems than their healthy siblings (25). Given that up to half of childhood survivors will suffer a therapy-related endocrinopathy, pediatric endocrinologists are frequently involved in their care and should be examining gonadal function and providing fertility counseling (26).

Chemotherapeutic agents, in particular alkylating agents, are well known to impact fertility in a dose-dependent fashion. Risk thresholds have decreased over time (e.g., decreasing from 10 to 7.5 to 4 grams/m^2 of cumulative cyclophosphamide dose for males), expanding the population that is considered to be "at-risk" (27).

Radiation exposure to the testicles or ovaries can also impact their function (28,29). The degree that function is affected depends on type of radiotherapy, the precise location, the dose given, and even the age of the patient at the time of therapy (28,29). Both alkylating agents and total body irradiation are commonly used in preparative regimens prior to hematopoietic stem cell transplantation (HSCT), resulting in gonadal insufficiency in up to 70–90% survivors (30,31). Finally, CNS radiotherapy can affect the hypothalamic-pituitary axis and result in precocious or delayed puberty/secondary hypogonadism (26). While fertility counseling is now considered standard of care for all patients with a new oncology diagnosis (32), fertility related discussions in survivorship are inconsistent and inadequate; in addition to distress and uncertainty about potential infertility, survivors have reported unplanned pregnancies due to misconceptions about infertility (33,34). Thus, practitioners providing care to childhood cancer survivors need to incorporate these discussions into routine clinical care.

HSCT and chemotherapeutic agents in non-malignant conditions

HSCT is also used in several hematologic and autoimmune conditions, such as sickle cell disease, aplastic anemia, thalassemia, and Wiskott-Aldrich syndrome. While degree of gonadotoxicity is variable based on exact preconditioning regimen, fertility is frequently threatened, thus a similar approach to counseling should be used before and after treatment as described for youth with cancer (35). Of note, other agents commonly used in these conditions, such as hydroxyurea for sickle cell disease, may also have an impact on fertility and reproductive health (36).

Similarly, alkylating agents such as cyclophosphamide may be used in various rheumatic and renal diseases, including systemic lupus erythematosus, vasculitis, and nephrotic syndrome, at gonadotoxic doses (37). Given that these patients are often treated with corticosteroids, pediatric endocrinologists are often involved in care due to adrenal suppression, growth concerns, and/or insulin resistance. Counseling about infertility risk and fertility preservation options has been lacking in these populations, and women with these conditions should also be counseled about birth control due to pregnancy related risks (37).

Gender dysphoria

Youth with gender dysphoria, defined as distress caused by incongruence between birth-assigned gender (based on genital anatomy) and affirmed/identified gender, are also at risk for treatment induced infertility. An increasing number of gender diverse children and adolescents are presenting to pediatric centers, and frequently seek hormonal interventions to alleviate this distress. Treatment guidelines state that infertility risk should be discussed and fertility preservation should be offered prior to gender-affirming medical and surgical interventions (38,39). As pediatric endocrinologists are often prescribing these medications, they should assume the primary responsibility for this counseling.

GnRH analogues, which are used to suppress puberty and its associated secondary sex characteristics, prevent the maturation of gametes. While these agents do not permanently impact fertility, an individual would not be able to pursue oocyte or sperm cryopreservation while on puberty suppression and many youth progress directly to testosterone or estrogen. Estrogen has been shown to impact sperm production, and there are also concerns about the impact of testosterone on fertility, though pregnancies have been reported after stopping testosterone (40,41). Given how little is known about fertility outcomes in individuals who have started these medications in adolescence, fertility preservation options should be discussed and referrals to reproductive endocrinologists (for oocyte cryopreservation) and sperm banking facilities (for sperm cryopreservation) should be offered. It should be noted that prior to oocyte collection, patients will need to undergo hormonal stimulation with female hormones, which in some individuals may result in emotional upset and undesired side effects (42). Along these same lines, human live births have only been reported with ovarian tissue reimplanted into the patient (heterotopically or orthotopically) which would also require stimulation. Despite treatment guidelines and an increasing number of studies demonstrating desire for biological parenthood among transgender adults, in two recent studies, <5% of transgender adolescents pursued fertility preservation even after counseling (41,43-46). More research is needed to examine fertility outcomes after hormonal interventions, perceived benefits and barriers of fertility preservation among these youth, and parenthood goals at different ages and developmental stages.

Impaired fertility related to underlying medical conditions

Differences of sex development

Disorders/differences of sex development (DSD) broadly encompass sex chromosome DSD, 46,XX DSD, 46,XY DSD, and ovotesticular DSD (47). While reproductive potential is highly variable in this group of conditions, this topic should routinely be addressed with all patients and families at the time of diagnosis and on an ongoing basis thereafter (47). Salient questions to address include: Are there gonads present that are likely to function in the future? In cases where a progressive decline in function may occur, should fertility preservation be considered in childhood or adolescence? Are there aspects of medical management that may impact future fertility? Additionally, if the gonads are being removed, a detailed discussion needs to occur regarding fertility implications (and other ethical and legal considerations) and whether there is a role for tissue preservation.

In some cases, such as testicular regression syndrome, testicular tissue is lost antenatally or soon after birth, resulting in complete infertility (48,49). At this point, there are no clear options to salvage reproductive potential for individuals with this condition and other disorders such as complete gonadal dysgenesis. However, there are some types of DSD previously thought to result in infertility where new possibilities have emerged with the use of fertility preservation and/or assisted reproductive technology. This group includes patients with Klinefelter syndrome (KS) and Turner syndrome (TS). Males with KS most commonly have a 47,XXY karyotype and impaired spermatogenesis (50). Historically these patients were all thought to be sterile. However, it has been found that some men with KS have a small number of cells that retain the ability to undergo spermatogenesis, and micro-TESE results in sperm retrieval in 50% of men with KS (50,51). With small studies showing no clear benefit of pursuing retrieval in adolescence, the current recommendation is to obtain an ejaculated sample as soon as possible after puberty begins (with cryopreservation of any viable sperm) and to offer micro-TESE at 15–30 years of age (52-54).

Individuals with TS most commonly have a 45,X karyotype, associated with hypoplastic ovaries and few oocytes, resulting in infertility (55). The oocyte damage occurs at variable rates ultimately ending with primary ovarian insufficiency (56). Some women may experience menarche and rare pregnancies have been reported; patients should be counseled about this possibility as well as the increased risk of fetal chromosomal abnormalities (56,57). Estrogen replacement therapy is typically utilized to enhance growth and development, induce puberty, and optimize bone health (56). This can be used in combination with *in vitro* fertilization of donor embryos in women with TS who wish to carry a pregnancy, though the high risk nature of the pregnancy and increased miscarriage rate should be considered (58). Unfortunately as the cause of infertility is lack of oocytes, fertility preservation remains challenging, though there have been reports of successful oocyte cryopreservation (59). It should be noted that there are women with mosaic TS, with a mixed karyotype of 45,X and most commonly 46,XX, who often have increased fertility potential (56,58). These patients are more likely to have a small number of oocytes at the onset of spontaneous puberty (56,57). Thus women with mosaic TS are most likely to benefit from fertility preservation and referrals to reproductive endocrinologists ought to take place without haste if puberty has already begun.

Fertility issues are also salient in other types of DSD. Both men and women with congenital adrenal hyperplasia (CAH) may experience fertility problems, with the extent depending on the severity of disease/disease control (60). In women, elevated androgens result in anovulatory cycles and polycystic ovarian syndrome (61). In men, elevated androgen feedback causes decreased gonadotropin production, ultimately resulting in a decrease in sperm production (61). Testicular adrenal rests are also common in males with CAH and are known to impact fertility; routine counseling and ultrasound screening has been recommended (62). Improving adherence to therapy is one way to reduce the infertility risk for both males and females, and males with testicular adrenal rests may also ultimately require TESE (63).

Fertility outcomes and preservation options for other types of DSD are more variable with minimal data to guide care. Androgen insensitivity syndrome (AIS) occurs in patients with 46,XY karyotypes and may range from partial to complete. Due to disease severity in complete AIS, testicles are poorly developed (60). There is significant phenotypic variability in partial AIS. Patients that are raised as female may undergo testicular removal resulting in infertility. Patients raised as male will retain their testicles, however still frequently suffer from poor fertility (60). Fertility is also impaired in other DSD such as rare forms of CAH, gonadal dysgenesis, and 5-alpha-reductase deficiency (64,65). However, a recent study showed that gonads removed from patients with a variety of DSD including AIS,

mixed gonadal dysgenesis, and ovotesticular DSD appeared to have viable germ cells, paving the way for future research and potential fertility preservation options (66).

Other causes of gonadal dysfunction

Other causes of primary ovarian insufficiency (POI) and premature menopause in females include genetic/metabolic conditions such as galactosemia and fragile X premutation (67). The mechanisms are not well understood (55), and counseling should focus on early preservation options. Autoimmune ovarian insufficiency should also be considered in females with spontaneous POI with no clear explanation, and is thought to be the etiology in ~5% of cases (68). This condition is more common in youth with other autoimmune conditions such as thyroid disease, Addison's disease, and type 1 diabetes; the most common autoimmune polyglandular syndromes (APS) are APS-1 (*AIRE* gene) and APS-2 (68). Adrenal (21-hydroxylase) and ovarian antibodies can help confirm the diagnosis. If detected prior to complete ovarian failure, oocyte collection could be an option for preservation. Polycystic ovarian syndrome, endometriosis, and pelvic surgery are all additional causes of fertility impairment.

Infiltrative conditions such as hemochromatosis can cause primary and secondary hypogonadism in males and females (55). Various infections can also lead to gonadal insufficiency; for example, mumps results in orchitis in select patients. The mechanism leading to decreased fertility is thought to be due to viral infection of the testicular tissue and resultant damage to the Sertoli and Leydig cells as well as testicular atrophy, however this is not completely understood (69-71). Approximately 13% of patients with mumps orchitis will have resultant subfertility, with infertility in a subset of these patients (71). Cryopreservation may be an option for those patients which retain partial spermatogenesis. Finally, there are other conditions such as type 1 diabetes and Down syndrome where fertility may be reduced, but less is known about fertility implications at this point (68).

Secondary hypogonadism

Conditions affecting the hypothalamic pituitary axis can result in secondary hypogonadism or hypogonadotropic hypogonadism. In these conditions, gonadal tissue has the potential to function normally, but is not receiving the appropriate hormonal stimulation. In men, this results in low testosterone and decreased sperm production and in women, low estrogen and absence of ovulation. This can be a congenital disorder, such as congenital GnRH deficiency, or acquired due to serious illness, infection or mass effect (72). Hormonal stimulation can be used to induce gonadal function for fertility purposes. Combinations of hCG and recombinant FSH can be used to initiate spermatogenesis in men, with gonadotropin/pulsatile GnRH therapy for inducing ovulation in women (73,74).

Ethical considerations

In the context of the four ethical pillars (autonomy, justice, beneficence, and non-maleficence), numerous ethical dilemmas may arise with regard to fertility counseling and preservation in pediatrics, many of which remain unresolved. *In the case of a minor, who should make the decisions about fertility preservation?* While guidelines from major pediatric organizations acknowledge parents as having this role, studies show that parents and youth often have differing opinions about fertility and reproductive health (2,75-77). *Shouldn't the ability to reproduce be a right shared by all?* In reality, assisted reproductive technology and fertility preservation are often costly and not covered by insurance, and thus unavailable to many people (78). *Should every child have the right to be informed about their fertility potential?* Pediatric guidelines stress the importance of age-appropriate disclosure about sensitive issues such as adoption, HIV status, and a new cancer diagnosis, yet many families are reluctant to address the possibility of future infertility with their children (79,80). *Could established or experimental fertility preservation procedures be exposing youth to harm, with or without sufficient hope for future benefit?* In some of the conditions described above, the fertility preservation procedure itself (due to hormonal stimulation or removal of tissue), and/or carrying a pregnancy, may potentially cause harm (81). Until more data are available, detailed discussions should occur with patients and families about potential risks versus benefits, and procedures such as TTC and OTC should be performed by experienced providers under an IRB-approved protocol. Additional challenges may arise in youth with cognitive limitations, psychiatric concerns, or a poor medical prognosis. Further, youth with genetic conditions that may be passed on to future biological children should be counseled about these risks in the context of fertility preservation discussions. Finally, policies vary with regard to disposition of stored gametes if the child passes away, with some centers mandating destruction and others allowing for youth to designate someone to take ownership (2).

Conclusions

As awareness grows about pediatric populations at risk for fertility impairment, the negative psychosocial impact of infertility, and advances in fertility preservation technologies, pediatric endocrinologists need to become educated and trained in addressing these issues (4). Studies show that timely fertility counseling results in higher rates of fertility preservation and improved satisfaction among patients and families (82,83). Further, adolescents and young adults state that they want health care providers to address these issues and help them navigate how to discuss their fertility status with friends and romantic partners (84). When possible, a multidisciplinary approach to fertility counseling and preservation is optimal, with inclusion of pediatric endocrinologists, oncologists (or whomever the primary treating provider is), urologists, gynecologists, reproductive endocrinologists, primary care providers, psychologists, and social workers.

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Footnote

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References

1. Rashidi B, Montazeri A, Ramezanzadeh F, et al. Health-related quality of life in infertile couples receiving IVF or ICSI treatment. BMC Health Serv Res 2008;8:186.
2. Fallat ME, Hutter J; American Academy of Pediatrics Committee on Bioethics, et al. Preservation of fertility in pediatric and adolescent patients with cancer. Pediatrics 2008;121:e1461-9.
3. Klosky JL, Anderson LE, Russell KM, et al. Provider influences on sperm banking outcomes among adolescent males newly diagnosed with cancer. J Adolesc Health 2017;60:277-83.
4. Nahata L, Ziniel SI, Garvey KC, et al. Fertility and sexual function: a gap in training in pediatric endocrinology. J Pediatr Endocrinol Metab 2017;30:3-10.
5. Irtan S, Orbach D, Helfre S, et al. Ovarian transposition in prepubescent and adolescent girls with cancer. Lancet Oncol 2013;14:e601-8.
6. Massarotti C, Scaruffi P, Lambertini M, et al. State of the art on oocyte cryopreservation in female cancer patients: A critical review of the literature. Cancer Treat Rev 2017;57:50-7.
7. Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril 2013;99:37-43.
8. Filatov MA, Khramova YV, Kiseleva MV, et al. Female fertility preservation strategies: cryopreservation and ovarian tissue in vitro culture, current state of the art and future perspectives. Zygote 2016;24:635-53.
9. Ladanyi C, Mor A, Christianson MS, et al. Recent advances in the field of ovarian tissue cryopreservation and opportunities for research. J Assist Reprod Genet 2017;34:709-22.
10. Zhou XH, Zhang D, Shi J, et al. Comparison of vitrification and conventional slow freezing for cryopreservation of ovarian tissue with respect to the number of intact primordial follicles: A meta-analysis. Medicine (Baltimore) 2016;95:e4095.
11. Jadoul P, Guilmain A, Squifflet J, et al. Efficacy of ovarian tissue cryopreservation for fertility preservation: lessons learned from 545 cases. Hum Reprod 2017;32:1046-54.
12. De Freytas-Tamura K. 'It's Like a Miracle': woman gives birth using ovary frozen since childhood. Available online: https://www.nytimes.com/2016/12/15/world/europe/its-like-a-miracle-woman-gives-birth-using-ovary-frozen-since-childhood.html
13. Luyckx V, Scalercio S, Jadoul P, et al. Evaluation of cryopreserved ovarian tissue from prepubertal patients after long-term xenografting and exogenous stimulation. Fertil Steril 2013;100:1350-7.
14. Blumenfeld Z, Katz G, Evron A. 'An ounce of prevention is worth a pound of cure': the case for and against GnRH-agonist for fertility preservation. Ann Oncol 2014;25:1719-28.
15. Lambertini M, Ceppi M, Poggio F, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol 2015;26:2408-19.
16. Sprauten M, Brydøy M, Haugnes HS, et al. Longitudinal serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels in a population-based sample of long-term testicular cancer survivors. J Clin Oncol 2014;32:571-8.
17. Eskenazi B, Wyrobek AJ, Sloter E, et al. The association

of age and semen quality in healthy men. Hum Reprod 2003;18:447-54.
18. Borges E Jr, Setti AS, Braga DP, et al. Decline in semen quality among infertile men in Brazil during the past 10 years. Int Braz J Urol 2015;41:757-63.
19. Shalet SM. Effect of irradiation treatment on gonadal function in men treated for germ cell cancer. Eur Urol 1993;23:148-51; discussion 152.
20. Rowley MJ, Leach DR, Warner GA, et al. Effect of graded doses of ionizing radiation on the human testis. Radiat Res 1974;59:665-78.
21. Adank MC, van Dorp W, Smit M, et al. 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.
22. Hagenäs I, Jørgensen N, Rechnitzer C, et al. 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;25:2031-8.
23. Brinster RL, Zimmermann JW. Spermatogenesis following male germ-cell transplantation. Proc Natl Acad Sci U S A 1994;91:11298-302.
24. Giudice MG, de Michele F, Poels J, et al. Update on fertility restoration from prepubertal spermatogonial stem cells: How far are we from clinical practice? Stem Cell Res 2017;21:171-7.
25. Chow EJ, Stratton KL, Leisenring WM, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol 2016;17:567-76.
26. Crowne E, Gleeson H, Benghiat H, et al. Effect of cancer treatment on hypothalamic-pituitary function. Lancet Diabetes Endocrinol 2015;3:568-76.
27. Green DM, Liu W, Kutteh WH, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. Lancet Oncol 2014;15:1215-23.
28. Overbeek A, van den Berg MH, van Leeuwen FE, et al. Chemotherapy-related late adverse effects on ovarian function in female survivors of childhood and young adult cancer: A systematic review. Cancer Treat Rev 2017;53:10-24.
29. Vakalopoulos I, Dimou P, Anagnostou I, et al. Impact of cancer and cancer treatment on male fertility. Hormones (Athens) 2015;14:579-89.
30. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer: a report from the st. jude lifetime cohort study. JAMA 2013;309:2371-81.
31. Frisk P, Arvidson J, Gustafsson J, et al. Pubertal development and final height after autologous bone marrow transplantation for acute lymphoblastic leukemia. Bone Marrow Transplant 2004;33:205-10.
32. Antal Z, Sklar CA. Gonadal function and fertility among survivors of childhood cancer. Endocrinol Metab Clin North Am 2015;44:739-49.
33. Canada AL, Schover LR. The psychosocial impact of interrupted childbearing in long-term female cancer survivors. Psychooncology 2012;21:134-43.
34. Zebrack BJ, Casillas J, Nohr L, et al. Fertility issues for young adult survivors of childhood cancer. Psychooncology 2004;13:689-99.
35. Dalle JH, Lucchini G, Balduzzi A, et al. State-of-the-art fertility preservation in children and adolescents undergoing haematopoietic stem cell transplantation: a report on the expert meeting of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) in Baden, Austria, 29-30 September 2015. Bone Marrow Transplant 2017;52:1029-35.
36. Smith-Whitley K. Reproductive issues in sickle cell disease. Hematology Am Soc Hematol Educ Program 2014;2014:418-24.
37. Nahata L, Sivaraman V, Quinn GP. Fertility counseling and preservation practices in youth with lupus and vasculitis undergoing gonadotoxic therapy. Fertil Steril 2016;106:1470-74.
38. Ethics Committee of the American Society for Reproductive Medicine. Access to fertility services by transgender persons: An Ethics Committee opinion. Fertil Steril 2015;104:1111-5.
39. Coleman E, Bochting W, Botzer M, et al. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. Int J Transgend 2012;13:165-232.
40. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2009;94:3132-54.
41. Wierckx K, Van Caenegem E, Pennings G, et al. Reproductive wish in transsexual men. Hum Reprod 2012;27:483-7.
42. Mitu K. Transgender reproductive choice and fertility preservation. AMA J Ethics 2016;18:1119-25.

43. De Sutter P, Kira K, Verschoor A, et al. The desire to have children and the preservation of fertility in transsexual women: A survey. Int J Transgend 2002;6:215-21.
44. Tornello SL, Bos H. Parenting intentions among transgender individuals. LGBT Health 2017;4:115-20.
45. Nahata L, Tishelman AC, Caltabellotta NM, et al. Low fertility preservation utilization among transgender youth. J Adolesc Health 2017;61:40-4.
46. Chen D, Simons L, Johnson EK, et al. Fertility preservation for transgender adolescents. J Adolesc Health 2017;61:120-3.
47. Hughes IA, Houk C, Ahmed SF, et al. Consensus statement on management of intersex disorders. J Pediatr Urol 2006;2:148-62.
48. Bader MI, Peeraully R, Ba'ath M, et al. The testicular regression syndrome--do remnants require routine excision? J Pediatr Surg 2011;46:384-6.
49. Hunter JD, Pierce SR, Calikoglu AS, et al. Embryonic testicular regression syndrome presenting as primary amenorrhea: a case report and review of disorders of sexual development. J Pediatr Adolesc Gynecol 2016;29:e59-62.
50. Corona G, Pizzocaro A, Lanfranco F, et al. Sperm recovery and ICSI outcomes in Klinefelter syndrome : a systematic review and meta-analysis. Hum Reprod Update 2017;23:265-75.
51. Fullerton G, Hamilton M, Maheshwari A. Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009? Hum Reprod 2010;25:588-97.
52. Plotton I, Giscard d'Estaing S, Cuzin B, et al. Preliminary results of a prospective study of testicular sperm extraction in young versus adult patients with nonmosaic 47,XXY Klinefelter syndrome. J Clin Endocrinol Metab 2015;100:961-7.
53. Nahata L, Yu RN, Paltiel HJ, et al. Sperm retrieval in adolescents and young adults with klinefelter syndrome: a prospective, pilot study. J Pediatr 2016;170:260-5.e1-2.
54. Nieschlag E, Ferlin A, Gravholt CH, et al. The Klinefelter syndrome: current management and research challenges. Andrology 2016;4:545-9.
55. Hirshfeld-Cytron J, Gracia C, Woodruff TK. Nonmalignant diseases and treatments associated with primary ovarian failure: an expanded role for fertility preservation. J Womens Health (Larchmt) 2011;20:1467-77.
56. Abir R, Fisch B, Nahum R, et al. Turner's syndrome and fertility: current status and possible putative prospects. Hum Reprod Update 2001;7:603-10.
57. Bernard V, Donadille B, Zenaty D, et al. Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. Hum Reprod 2016;31:782-8.
58. Grynberg M, Bidet M, Benard J, et al. Fertility preservation in Turner syndrome. Fertil Steril 2016;105:13-9.
59. Oktay K, Bedoschi G. Oocyte cryopreservation for fertility preservation in postpubertal female children at risk for premature ovarian failure due to accelerated follicle loss in Turner syndrome or cancer treatments. J Pediatr Adolesc Gynecol 2014;27:342-6.
60. Van Batavia JP, Kolon TF. Fertility in disorders of sex development: A review. J Pediatr Urol 2016;12:418-25.
61. Choi JH, Yoo HW. Management issues of congenital adrenal hyperplasia during the transition from pediatric to adult care. Korean J Pediatr 2017;60:31-7.
62. Claahsen-van der Grinten HL, Otten BJ, Stikkelbroeck MM, et al. Testicular adrenal rest tumours in congenital adrenal hyperplasia. Best Pract Res Clin Endocrinol Metab 2009;23:209-20.
63. King TF, Lee MC, Williamson EE, et al. Experience in optimizing fertility outcomes in men with congenital adrenal hyperplasia due to 21 hydroxylase deficiency. Clin Endocrinol (Oxf) 2016;84:830-6.
64. Marsh CA, Auchus RJ. Fertility in patients with genetic deficiencies of cytochrome P450c17 (CYP17A1): combined 17-hydroxylase/17,20-lyase deficiency and isolated 17,20-lyase deficiency. Fertil Steril 2014;101:317-22.
65. Kang HJ, Imperato-McGinley J, Zhu YS, et al. The effect of 5 alpha-reductase-2 deficiency on human fertility. Fertil Steril 2014;101:310-6.
66. Finlayson C, Fritsch MK, Johnson EK, et al. Presence of germ cells in disorders of sex development: implications for fertility potential and preservation. J Urol 2017;197:937-43.
67. Sullivan SD, Welt C, Sherman S. FMR1 and the continuum of primary ovarian insufficiency. Semin Reprod Med 2011;29:299-307.
68. Komorowska B. Autoimmune premature ovarian failure. Prz Menopauzalny 2016;15:210-4.
69. Wu H, Shi L, Wang Q, et al. Mumps virus-induced innate immune responses in mouse Sertoli and Leydig cells. Sci Rep 2016;6:19507.
70. Wang XX, Ying P, Diao F, et al. Altered protein prenylation in Sertoli cells is associated with adult infertility resulting from childhood mumps infection. J Exp Med 2013;210:1559-74.
71. Davis NF, McGuire BB, Mahon JA, et al. The increasing incidence of mumps orchitis: A comprehensive review. BJU Int 2010;105:1060-5.
72. Nachtigall LB, Boepple PA, Pralong FP, et al. Adult-onset

idiopathic hypogonadotropic hypogonadism--a treatable form of male infertility. N Engl J Med 1997;336:410-5.
73. Liu PY, Baker HW, Jayadev V, et al. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. J Clin Endocrinol Metab 2009;94:801-8.
74. Martin KA, Hall JE, Adams JM, et al. Comparison of exogenous gonadotropins and pulsatile gonadotropin-releasing hormone for induction of ovulation in hypogonadotropic amenorrhea. J Clin Endocrinol Metab 1993;77:125-9.
75. Quinn GP, Stearsman DK, Campo-Engelstein L, et al. Preserving the right to future children: An ethical case analysis. Am J Bioeth 2012;12:38-43.
76. Quinn GP, Knapp C, Murphy D, et al. Congruence of reproductive concerns among adolescents with cancer and parents: pilot testing an adapted instrument. Pediatrics 2012;129:e930-6.
77. Klosky JL, Simmons JL, Russell KM, et al. Fertility as a priority among at-risk adolescent males newly diagnosed with cancer and their parents. Support Care Cancer 2015;23:333-41.
78. Johnson EK, Finlayson C, Rowell EE, et al. Fertility preservation for pediatric patients: current state and future possibilities. J Urol 2017;198:186-94.
79. Committee on Pediatric AIDS. Disclosure of illness status to children and adolescents with HIV infection. American academy of pediatrics committee on pediatrics AIDS. Pediatrics 1999;103:164-6.
80. Sutton EJ, Young J, McInerney-Leo A, et al. Truth-telling and turner syndrome: the importance of diagnostic disclosure. J Pediatr 2006;148:102-7.
81. Backhus LE, Zoloth L. Oncofertility Fertility Preservation for Cancer Survivors. Woodruff TK, Snyder KA. eds. Springer US, 2007:163-79.
82. Klosky JL, Anderson LE, Russell KM, et al. Provider influences on sperm banking outcomes among adolescent males newly diagnosed with cancer. J Adolesc Health 2017;60:277-83.
83. Kelvin JF, Thom B, Benedict C, et al. Cancer and fertility program improves patient satisfaction with information received. J Clin Oncol 2016;34:1780-6.
84. Sanders C, Carter B, Lwin R. Young women with a disorder of sex development: Learning to share information with health professionals, friends and intimate partners about bodily differences and infertility. J Adv Nurs 2015;71:1904-13.

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