Fertility Issues in Pediatric Urology

Kathleen Kieran, MD, MS, MME*, Margarett Shnorhavorian, MD, MPH

KEYWORDS

• Fertility • Oncology • Differences in sexual differentiation • Pediatric

KEY POINTS

- Improved understanding of the pathophysiology of many medical and surgical conditions and the mechanisms of action and side effects of pharmaceutical agents have identified opportunities to recognize and mitigate.
- Although pediatric urologists should be aware of the many causes of and treatment for fertility concerns, a multidisciplinary, patient-centered approach is crucial to helping providers, patients, and families identify and achieve fertility goals.
- Threats to potential fertility can arise at any point along the hypothalamic-pituitary-gonadal axis, or may be the result of direct end-organ damage.

Although infertility was once considered a disease of adults, improved understanding of the pathophysiology of many medical and surgical conditions and the mechanisms of action and side effects of pharmaceutical agents have identified opportunities to recognize and mitigate potential barriers to fertility at an earlier age, in some cases even before puberty. Despite the fact that many factors influencing fertility arise in children, many pediatric and early-career specialists are not comfortable discussing fertility concerns with patients.[1] This may lead to absent or incorrect information provided to patients and families, and missed opportunities to preserve fertility in time-sensitive settings. Although pediatric urologists should be aware of the many causes of and treatment for fertility concerns, a multidisciplinary, patient-centered approach is crucial to helping providers, patients, and families identify and achieve fertility goals.

In adults, "infertility" is defined as the inability to conceive a child after 1 year of unprotected intercourse, or 6 months if the female partner is older than 35.[2] In the pediatric population, many of whom have not reached sexual maturity and/or are less likely to have attempted conception, fertility concerns are better characterized as changes in fertility potential. These threats to potential fertility can arise at any point along the hypothalamic-pituitary-gonadal axis, or may be the result of direct end-organ damage. Although altered fertility potential can arise from multiple causes, those most relevant to pediatric urologists are described in this article.

Although an evolving understanding of the underlying mechanisms of and optimal treatments for potentially altered fertility mandates that this list should not be considered exhaustive, it provides a reference point for pediatric urology providers caring for these children.

FERTILITY CONSIDERATIONS IN PEDIATRIC ONCOLOGY PATIENTS

Fertility preservation is an increasingly important topic in the treatment of pediatric cancers as

Disclosure: None.

Division of Urology, Seattle Children's Hospital, 4800 Sand Point Way Northeast, OA.9.220, Seattle, WA 98105, USA

* Corresponding author. Division of Urology, Seattle Children's Hospital, 4800 Sand Point Way Northeast, OA. 9.220, Seattle, WA 98105.

E-mail address: kathleen.kieran@seattlechildrens.org

Urol Clin N Am 45 (2018) 587–599

https://doi.org/10.1016/j.ucl.2018.06.006

survival rates have improved and quality of life, particularly related to late effects, has become a focal point for survivors and their families.[3–5] Surgical intervention (eg, prostatectomy or orchiectomy), chemotherapy (particularly alkylating agents), and radiotherapy (especially cranial or testicular) have all been implicated in altered fertility in patients with childhood cancer. Replacement of gonads by tumor (as in **Fig. 1**) may also negatively impact fertility potential. Fertility compromise in the oncologic setting can arise from alterations at the hormonal (steroidogenic) or end-organ levels.[6–8] Hormonal derangements can arise at the hypothalamic, pituitary, or gonadal levels; in one series, one-quarter of childhood cancer survivors had hypogonadism (defined as elevations in serum follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), as did more than one-third of survivors of testicular cancer.[9] Patients undergoing bone-marrow transplantation, particularly myeloablative regimens incorporating whole-body radiotherapy, are also at high risk of fertility loss; myeloablative regimens are associated with high rates of ovarian failure, whereas one-third of women receiving nonmyeloablative regimens in one study had successful pregnancies following treatment.[10,11]

Within the testis, spermatogenesis is more likely to be disrupted than steroidogenesis owing to the differential sensitivity of the germinal epithelium (which fosters sperm maturation) to cytotoxic agents compared with the Leydig cells, which secrete testosterone.[12] The direct and dose-dependent gonadal toxicity of chemotherapeutic agents is best understood for alkylating and alkylatinglike agents (eg, cyclophosphamide, chlorambucil, busulfan).[7,8,13–16] Much less robust data are available regarding the impact of contemporary chemotherapy regimens on spermatogenesis and steroidogenesis. In particular, limited fertility data are available for cisplatin, which comprises the backbone of modern chemotherapeutic regiments for common childhood cancers, including germ cell tumors, osteosarcoma, Ewing sarcoma, and central nervous system malignancies; however, exposure to these agents is associated with lower pregnancy rates for male but not female cancer survivors compared with sibling controls.[17] Although exposure to platinum-based chemotherapy, particularly over multiple cycles, is associated with a 17-fold increased risk of hypogonadism in testicular cancer survivors,[9] much less is known about the spermatogenic and steroidogenic effects of platinum-based chemotherapy in non–germ cell patients. Similar studies of patients receiving ifosfamide alone or in combination with cisplatin are also plagued by small numbers, variability in treatment regimens, inconsistent semen analysis collection, and lack of healthy controls for comparison.[18–20] Bleomycin has been correlated with impaired fertility in some studies.[21]

One promising avenue to understand how exposure to chemotherapy may lead to alterations in fertility is differential methylation of spermatozoal DNA. In normal spermatogenesis, DNA methylation of specific loci is known to play a role in germ cell development[22,23]; variations in DNA methylation patterns have been associated with decreased sperm counts and clinically decreased fertility.[24,25] Altered (both hyper- and hypo-) methylation patterns have been observed in animal models exposed to multiple antineoplastic agents, including cyclophosphamide; these changes persist in future generations, supporting the ability of chemotherapeutic agents to induce an epigenetic shift through differential spermatozoal DNA methylation patterns.[26,27] Differential DNA methylation patterns in chemotherapy-exposed cancer survivors suggest that oncologic treatment may have the potential to influence epigenetic inheritance.[28]

Female patients with cancer may also have fertility challenges arising after chemotherapy,

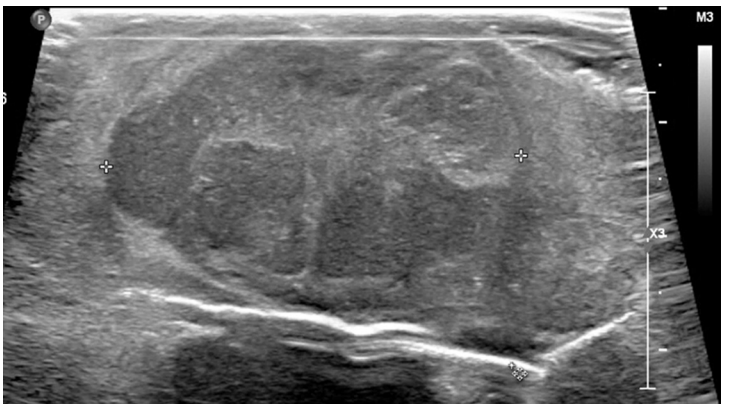

Fig. 1. Testis replaced by leukemia in post-chemotherapy relapse.

radiation therapy, or pelvic surgery. Premature ovarian failure is described as the loss of ovarian function before the age of 40.[29] Unlike testes, which constantly generate new spermatozoa, ovaries have a maximal number of follicles at birth and thus the supply of oocytes cannot be replenished.[30] Like the testis, the ovarian follicles are exquisitely sensitive to the effects of alkylating agents; compared with alternative chemotherapy regimens, those involving alkylating agents are 4 times as likely to be associated with gonadal injury, although platinum-based and other nonalkylating regimens should not be considered to be completely free from potential gonadal toxicity.[31]

Both oocyte cryopreservation and ovarian tissue cryopreservation are options for preservation of fertility in female patients being treated for cancer.[32–35] Oocyte cryopreservation is beneficial in that only oocytes (and not gonadal tissue) are harvested, but to do so requires ovarian stimulation, a process that can take several weeks and may delay the initiation of oncology treatment. Ovarian tissue cryopreservation can be offered to all patients and does not require a delay or hyperstimulation, but carries the risk of potentially preserving neoplastic cells (if any are present within the ovary), as well as failure of the immature follicles contained in ovarian tissue to mature properly. Even when fertilization can be successfully achieved, female patients may not have a uterus capable of carrying a child to term: pelvic radiation or surgery may damage the uterine lining, compliance, and vasculature.[31,36]

As the mechanisms of fertility changes in childhood cancers are further elucidated, fertility preservation through the acquisition and storage of testicular tissue and/or semen samples remains an option for patients and their families. For fertility preservation programs to be successful, however, tissue must be collected before the start of treatment; this requires a motivated and educated provider who recognizes the need to discuss fertility preservation at an often emotionally charged time, as well as a family (and patient) with the interest in and financial resources to preserve genetic material. One particular challenge is the potentially prolonged period between cancer treatment and desired fertility; for example, one study[37] found that although 80% of newly diagnosed adolescents and young adult oncology patients were interested in biologic parenthood, fewer than one-third ranked having a child as a significant life goal, and fewer than half had discussed fertility with their physician. Another study found that patients without insurance, female patients, those receiving treatment regimens classified as "low risk" to fertility, and those raising children younger than 18 years were less likely to discuss fertility preservation with providers and to make arrangements for fertility preservation.[38] In one study, only approximately 1 in 4 pediatric oncologists routinely referred pubertal female patients for consideration of fertility preservation.[39]

Because children with cancer are younger than the age of consent, parental values and desires may influence treatment choices, including fertility preservation. Although parents are charged with acting in their child's best interest, the priorities of parents and children may not be identical,[40] although discerning whether this is a true difference in values can be challenging. However, one study[41] of cancer survivors found uniform value placed on fertility preservation by both patients and parents. These findings underscore the need for fertility preservation to be uniformly offered to all newly diagnosed patients regardless of cost, for provider education on fertility preservation at a patient-appropriate level, and to use a multidisciplinary approach wherein the responsibility for discussing fertility considerations does not fall on a single provider. Many of the pitfalls and challenges of fertility preservation can be avoided with a standardized process of care[42] even soon after diagnosis, many families will choose to pursue sperm or tissue banking and are satisfied with the process.[43] The American Society for Clinical Oncology published guidelines for fertility preservation in patients with cancer in 2006 and updated these guidelines in 2013; the most current version of the guidelines encourages active assessment of patient/family interest in fertility preservation, referral of interested and ambivalent patients to fertility specialists, and collection and banking of appropriate tissue at the earliest available opportunity (ideally before the initiation of treatment).[44] There are no guidelines on how long banked tissue should be preserved, particularly if the donor patient has died[45]; although this debate is beyond the scope of this article, providers should be aware that simply collecting and banking tissue is not an endpoint for patients and families.

FERTILITY PRESERVATION IN PEDIATRIC PATIENTS WITH DIFFERENCES IN SEX DEVELOPMENT

Addressing fertility concerns of individuals and families with differences in sex development (DSD), given the heterogeneity of this group of patients, ideally is based on genetic and molecular as well as anatomic understanding of each individual with a DSD. DSD is the current nomenclature for patients in whom the chromosomal sex (eg, XX or XY) differs from the gonadal and/or phenotypic

sex. DSDs are generally stratified chromosomally: 46,XX; 46,XY; and other abnormalities of sex chromosomes, such as Klinefelter syndrome (47,XXY) and Turner syndrome (45,XO). Abnormal tissue receptivity (complete and partial androgen insensitivity syndrome) are also considered forms of DSD.

The most common cause of DSD is congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (salt-wasting and non–salt-wasting), an autosomal recessive condition; 11-beta-hydroxylase deficiency is the second most common subtype of CAH. In this condition, the increased androgen production as a result of insufficient enzyme levels results in masculinization of 46,XX female individuals (**Fig. 2**); in 46,XY male individuals, the phenotype may be less apparent. Impaired fertility is more common in the salt-wasting variant of 21-hydroxylase deficiency and in 11-beta-hydroxylase deficiency, but improved fertility rates can be achieved with suppression of adrenal hormones through exogenous mineralocorticoid administration, thereby relieving the suppression of the hypothalamic-pituitary-gonadal axis and promoting ovulation.[46–49] Male individuals with CAH may also develop adrenal rests that can enlarge and sterically block the reproductive tract.[46,47] Patients with less common, more severe abnormalities of steroid synthesis, such as 3-beta-hydroxysteroid dehydrogenase deficiency, StAR (steroidogenic acute regulatory) protein deficiency, and abnormalities of cytochrome P450 enzymatic pathways, are generally considered infertile.[50–52]

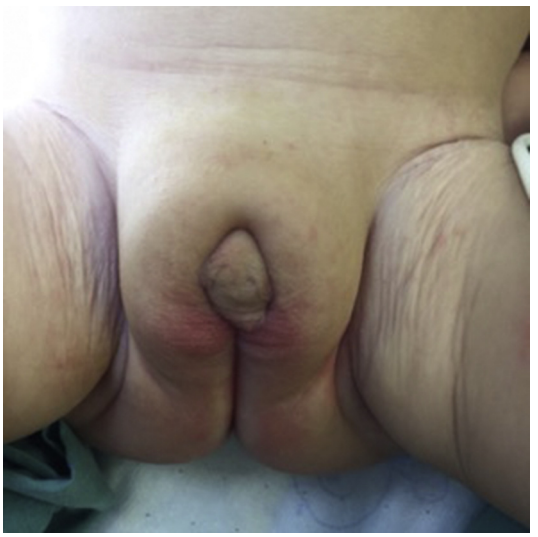

Fig. 2. Masculinized female individual with classic CAH (21-hydroxylase deficiency). Note enlarged clitorophallic structure.

Undervirilization of 46,XY male individuals (**Fig. 3**) may also be secondary to defects in testosterone biosynthesis, in Leydig cell hypoplasia or failure, or in reduced or absent androgen receptivity of target tissue. Patients with inability to endogenously synthesize testosterone are typically infertile, although paternity has been reported in one patient with Leydig cell hypoplasia in whom sperm harvesting was performed after human chorionic gonadotropin (hCG) stimulation.[53–55] Complete androgen insensitivity syndrome typically presents as a phenotypic female without Mullerian structures and with a blind-ending vagina. Histopathology of testes in these patients shows Leydig cell hyperplasia (consistent with increased testosterone secretion in the absence of an intact feedback loop), local fibrosis, and a decreased number of Type Ad spermatogonia.[56] Removal of these gonads following puberty is discussed owing to the increased risk of neoplasia; thus, making fertility potential an important topic of discussion before surgery. Partial androgen insensitivity and 5-alpha reductase insensitivity syndromes have a broader range of phenotypes commensurate with variations in local tissue sensitivity, but abnormal development of Wolffian structures and poor spermatogenesis secondary to

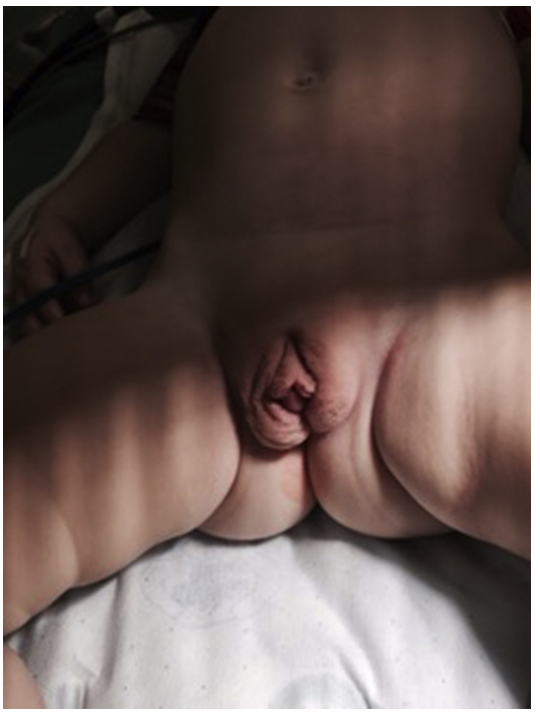

Fig. 3. Patient with partial androgen insensitivity syndrome. Note penoscrotal transposition, poorly rugated and underdeveloped scrotum. This patient also has penoscrotal hypospadias (not pictured).

limited androgen activity may compromise fertility.[57–59] Testes in these patients have a much higher risk of malignant transformation and thus gonadectomy at the time of diagnosis in patients reared female or shortly after puberty in those reared male is recommended.[60]

Ovotesticular DSD is associated with the presence of both ovarian and testicular tissue. In some cases, one of each gonad is present, and in other cases, and ovotestis (both ovarian and testicular tissue in the same gonad). Fertility potential largely reflects the integrity of the internal genitalia; ovarian tissue is often adequate for ovulation, although most children with this condition are raised male.[61,62] However, the risk of gonadoblastoma in ovotestes often prompts consideration for early gonadectomy, which may negatively impact future fertility.[60]

Individuals with DSDs are at risk for hypogonadism that increase their risk of infertility. Male individuals with a 46,XX genotype usually have testes, but these testes have no Leydig cells and no spermatogenesis, and these men are considered infertile.[53,63] Male individuals with Klinefelter syndrome (genotype 47,XXY) typically present with a tall, thin body habitus as well as smaller, firmer testicles at puberty, although many patients will have subtle presentations and may remain undiagnosed. Men with Klinefelter syndrome have low serum testosterone levels but elevated levels of pituitary hormones (LH and FSH), and typically have small, firm testes developing as germ cells are lost beginning in early childhood and replaced with firmer fibrotic tissue[64,65]; as a result, most men with this syndrome have abnormally low or absent sperm counts on semen analysis. Although sperm can be found, microscopically extracted, and preserved (or used for intracytoplasmic injection) in approximately half of patients with Klinefelter syndrome, there is continued debate about whether this procedure should be routinely offered to young men with this condition.[66,67] As with other conditions in which sperm banking should be considered, the interest in and knowledge of future fertility by the adolescent patient and his family, as well as cost, are important considerations for providers and families.

Streak gonads, associated with gonadal failure, have been reported in Turner syndrome (genotype 45,XO) and in mixed gonadal dysgenesis (variable genotype). In Turner syndrome, patients are phenotypically female but have few ovarian follicles at birth. The ovarian failure also necessitates exogenous estrogen replacement in most patients. Women with this condition are often able to bear children with assisted reproductive techniques (eg, donor oocyte and embryo transfer), but may have high-risk pregnancies owing to comorbid cardiovascular conditions associated with Turner syndrome.[68,69] Patients with mixed gonadal dysgenesis typically have hyalinized gonads, few Leydig cells (thus necessitating testosterone supplementation for puberty), and very low to absent spermatogenesis, and are generally considered infertile.[70,71]

FERTILITY CONSIDERATIONS IN TRANSGENDER YOUTH

The care of transgender patients, particularly in the adolescent age group, is an emerging focus for primary care and specialty providers. Although diversity of self-described gender is not a new concept, until recently most patients undergoing gender-affirming procedures (medical or surgical) were adults. The emergence of transgender health care in the adolescent age group has underscored the importance of proactively discussing fertility with these patients. As with pediatric oncology patients, both oocyte cryopreservation and sperm banking, as well as ovarian or testicular cryopreservation (both investigational), may be offered.[72] A minority of gender-diverse and sex-diverse adolescents report having conversations regarding fertility preservations with their providers, although at least 25% to 50% of these patients indicate an interest in preserving fertility and most want to know more about fertility preservation.[73,74] In one study, only 12.8% of patients were referred for conversations regarding fertility preservation, of whom 38.5% went on to use fertility preservation techniques.[75] Timely discussion of fertility preservation options is especially important in these patients, as many gender-diverse children experience significant emotional distress at puberty when secondary sex characteristics that are not congruent with the self-identified gender begin to develop; hormonal suppression (eg, histrelin implants) can successfully delay pubertal development both externally and at the gonadal level. Similarly, exogenous hormones administered to promote the development of gender-congruent secondary sexual characteristics will further suppress endogenous gonadotropins, although preservation of ovarian follicles and maturation is seen even after prolonged androgen exposure.[76] As with oncologic therapies, cost, provider knowledge, and desire to promptly initiate therapy have also been identified as reasons that fertility preservation was not pursued.[75] Finally, gender-affirming surgery (including gonadectomy, vaginoplasty, hysterectomy, or phalloplasty) may limit the future reproductive options available to transgender persons.

GONADOTOXIC DRUGS

Successful treatment of many nononcologic medical conditions involving increased immune system activity involves drugs that dampen the immune response and limit cellular division. Notably, liver and kidney failure may result in impaired fertility secondary to influence on the hypothalamic-pituitary-gonadal axis, with fertility restored approximately 1 year after transplantation.[77,78] In particular, pharmaceuticals used for organ transplantation and rheumatologic diseases may have adverse effects on fertility.[79–81] Women with rheumatoid arthritis tend to have prolonged time to conception (only approximately 50%–75% are able to conceive within 1 year of unprotected intercourse), earlier menopause, and elevated levels of anti-Mullerian hormone.[82–84] The effects of the disease and the treatment are difficult to tease apart, because difficulty conceiving and abnormal hormone levels are more prevalent during disease flares, and some investigators have postulated that women with rheumatologic diseases are less likely to be sexually active during periods of more acute disease severity.[82] Regardless of the independent contribution of the disease process, numerous categories of drugs used for treatment of rheumatologic conditions have been associated with impaired fertility. Alkylating agents, such as cyclophosphamide, can cause permanent gonadal damage. The anti-prostaglandin effect of nonsteroidal anti-inflammatories may impair spermatogenesis, although the consistency and reversibility of adverse gonadal effects is not well described.[85,86] Corticosteroids may adversely affect fertility by blocking inflammatory pathways and also by direct feedback on the hypothalamic-pituitary-gonadal axis, but are not consistently associated with decreased sperm counts.[85,87,88] Similarly, methotrexate, chloroquine, and tumor necrosis factor inhibitors all have postulated mechanisms of action that may impair fertility, but semen analyses in patients on these medications has not shown a consistent negative effect on sperm production.[85,87,88] Interestingly, although stem cell transplantation (particularly after irradiation) has been found to correlate with impaired fertility in oncology patients, patients undergoing stem cell transplantation for autoimmune disease fared better: in one study, 36% of women were able to achieve pregnancy, and no patients suffered premature gonadal failure.[89]

Literature on education regarding fertility preservation in adolescents with rheumatologic diseases undergoing potentially gonadotoxic therapy is lacking. One study found that fewer than half of patients had conversations regarding fertility preservation documented in the medical chart; in this study, fewer than 25% of men were offered sperm banking, and female individuals were offered only hormonal therapy with leuprolide acetate for fertility preservation.[90] These findings support the need for providers to initiate conversations about fertility preservation with adolescent patients in these settings.

VARICOCELES IN PEDIATRIC AND ADOLESCENT BOYS

Varicoceles, or dilated veins in the pampiniform plexus that drains the testicle, are increasingly common in adolescents and even in prepubertal children. Although prevalence estimates are widely variable, approximately 1 in 6 teen boys will be diagnosed with a varicocele.[91,92] The relative venous stasis (**Fig. 4**) associated with varicoceles has been associated with an increase in local temperature in the ipsilateral (and to a lesser degree the contralateral) testis; because optimal spermatogenesis occurs within a narrow temperature window, this excess heat may be associated with decreased sperm production. Oxidative stress and changes in blood flow in and around the testis may be associated with the altered

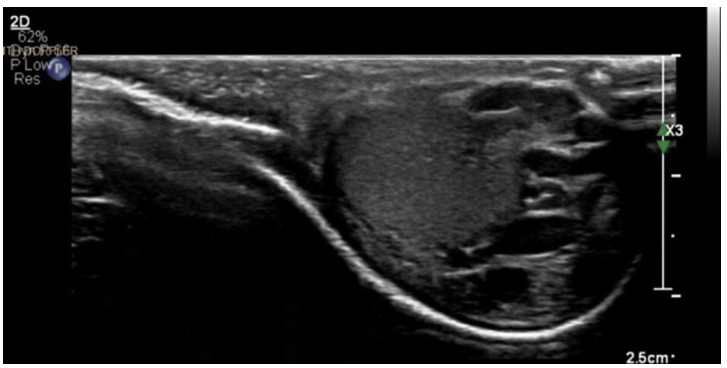

Fig. 4. Grade 3 varicocele in adolescent boy. Note enlarged caliber of pampiniform plexus.

semen parameters and decreased DNA quality observed in the testes of men with varicoceles. Although the precise mechanisms remain unknown, surgical repair has been associated with improvement in semen parameters and DNA fragmentation in some series.[93,94]

Although more than 1000 articles have been published on the topic of adolescent varicoceles, there is ongoing debate regarding whether (and when) to repair varicoceles in pediatric patients. In adults, abnormal semen parameters and a substantial (>15%) variation in testicular size are indications for repair. However, these indications are less clear cut in adolescents who may still be growing (and for whom transient, not permanent, testicular asymmetry may represent a normal pattern of growth) and for whom fertility has not yet been assessed. Published literature on adolescent varicoceles also has few randomized studies, but many meta-analyses; the consistency of data collection in the various studies included in many meta-analyses is variable, with patient Tanner stage, objective testicular measurements, and semen analysis data often limited or missing.[95] The lack of consistent data collection across studies included in meta-analyses makes drawing definitive conclusions difficult and likely contributes to some of the clinical confusion surrounding varicocele management.

Although semen analyses are recommended during the evaluation of adolescents with varicoceles, only approximately 1 in 8 pediatric urologists routinely obtain semen analyses in such patients, with practitioner and family discomfort and lack of patient knowledge cited as the most common reasons that semen analyses were not obtained.[96] Even in patients for whom semen analyses were obtained, there are currently no standard parameters akin to the World Health Organization guidelines for adult semen analyses, making interpretation difficult and limiting the utility of the test for clinical planning. Despite this, at least one meta-analysis suggests that the presence of a varicocele in adolescence is associated with decreased sperm concentration and altered sperm characteristics (motility and morphology), and that surgical intervention is associated with an improvement in sperm concentration and motility on serial semen analyses.[97] However, the relationship between testicular asymmetry and abnormal semen parameters has been well documented. Patients with symmetric testes are less likely to have poorer semen parameters over time, and varicocelectomy appears to have beneficial effects on “catch-up” growth for patients with greater than 10% testicular asymmetry.[98,99]

Although testicular size and semen parameters appear to be correlated, the inconsistent findings in meta-analyses and individual studies suggests that a third factor may modify his relationship. Although this modifying factor has not been identified, one candidate is testosterone production. Meta-analyses assessing serum testosterone levels in men with varicoceles before and after surgical intervention have found decreased testosterone levels preoperatively compared with healthy controls, and often (but not always) improved serum testosterone levels after surgical correction of the varicocele.[100,101] However, these data should be considered in light of the facts that few studies consistently measure serum testosterone, variations in testosterone level do not necessarily correlate with preoperative severity of the varicocele or postoperative improvement in semen parameters, and some men actually had decreased serum testosterone levels following surgical repair. A prospective study[102] assessing hormone levels and fertility in men with varicoceles and a median age of 19 years found no differences in serum testosterone levels, but did find that the men with varicoceles had lower levels of inhibin-B and increasing levels of LH and FSH, as well as more abnormal semen parameters, compared with healthy controls. The severity of the hormonal derangements and abnormal semen parameters increased in higher-grade varicoceles. Again, the variability in clinical results reported in studies included in meta-analyses and in individual prospective studies likely reflects the content and quality of the data collected in each study.

The potentially protracted period between surgical intervention and attempts at fertility further cloud the picture of whether varicocelectomy provides clinical benefits to future fertility in teenagers. One study[103] of more than 400 young men with palpable varicoceles found that, after a mean 16-year follow-up, the fertility rate was 77.3% in those who had undergone repair, compared with 48.4% of those who had not. Mean time to conception was also significantly shorter (11.2 vs 16.9 months) in those men who had undergone surgical repair compared with those who had not. Although this study was performed at a single institution with a single surgeon and had more than 16 years of follow-up, there was no randomization (patients were allowed to choose whether or not to pursue surgical intervention), and nearly two-thirds of patients had bilateral varicoceles, which may have a different natural history than unilateral disease.

FERTILITY CONSIDERATIONS IN PEDIATRIC PATIENTS WITH CRYPTORCHIDISM

Cryptorchidism, or undescended testes, affects approximately 1% to 2% of male individuals after term birth; by the age of 3 months, almost all of these testes will have descended spontaneously into the scrotum.[104] The incidence of cryptorchidism is higher in premature infants.[105] Cryptorchidism has been consistently associated with an adverse effect on fertility parameters, including decreasing number of germ cells and smaller size of the cryptorchid testis in the first several years of life (although these 2 parameters are not necessarily correlated).[106] The decreased number of germ cells is thought to arise from a lower rate of development of Type Ad (dark) spermatogonia from gonocytes.[107] Early orchidopexy (**Fig. 5**), ideally between the ages of 6 months and 1 year, is currently recommended to preserve fertility in these patients.[108] Later age at definitive surgical repair has also been found to correlate with more abnormal hormone (FSH and LH) levels and abnormal semen analyses in adulthood.[109] Importantly, children with syndromes associated with increased risk of cryptorchidism (eg, Prader-Willi syndrome) may be at increased risk of fertility issues despite surgical treatment in keeping with current best practices.[110] In the past, hormonal treatment with hCG or gonadotropin-releasing hormone (GnRH) was offered as a nonsurgical option for treatment of undescended testicles; however, this approach is no longer recommended to facilitate descent,[108] although GnRH has been shown to be associated with changes in the expression of genes within the hypothalamic-pituitary-gonadal axis, which directly influences fertility.[111]

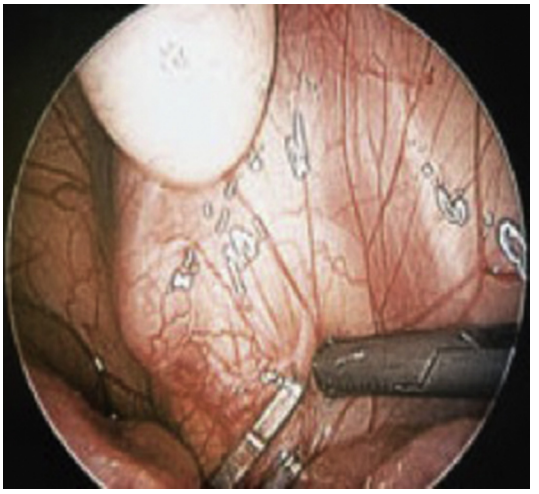

Fig. 5. Early orchidopexy is important for fertility preservation, especially for intra-abdominal testes.

Recent research[112] has demonstrated that the concentration of Type Ad spermatogonia, but not germ cells, in unilateral cryptorchid testes is associated with differences in sperm count and quality on adult semen analysis. Although patients with decreased concentrations of Type Ad spermatogonia continued to have FSH levels and sperm concentrations and motility that were within the normal range, FSH levels were significantly higher and sperm concentrations and motility significantly lower than levels seen in patients with unilateral cryptorchidism but normal concentrations of Type Ad spermatogonia. In patients with bilateral cryptorchidism, hormone levels and sperm characteristics in adulthood were abnormal in patients with decreased concentrations of Type Ad spermatogonia, but these levels were not significantly different from those of patients with bilateral cryptorchidism and normal concentrations of Type Ad spermatogonia. Sperm density was significantly decreased in patients with bilateral undescended testes and decreased concentrations of Type Ad spermatogonia. The investigators concluded that the unilateral and bilateral undescended testes may have differential sensitivity to the development of endocrinopathy, and that the concentration of Type Ad spermatogonia per tubule (at the time of orchidopexy) is a better predictor of adult fertility parameters than the concentration of germ cells per tubule.

HYPOGONADISM IN ADOLESCENTS

Hypogonadism arises when the testicles are unable to produce adequate testosterone for normal endocrinologic and sustentacular function. Hypogonadism may be primary (failure of testosterone production at the testis level), secondary (low levels of gonadotropins secreted by the pituitary), or tertiary (failure of GnRH to be released at the hypothalamic level).[113] In all 3 cases, the end result is low testosterone production by the testis, but the 3 subtypes are distinguished by variations in early-morning of the hypothalamic and pituitary hormones. A diagnosis of hypogonadism should prompt further evaluation for metabolic syndrome and osteoporosis.[114] Hypogonadism in DSD was discussed earlier.

Hypogonadotrophic hypogonadism is associated with decreased levels of hypothalamic hormones (GnRH), pituitary hormones (FSH and LH), and testis-derived androgens (testosterone), and typically arises when there is some type of damage at the hypothalamic level, such as congenital hypogonadotrophic hypogonadism (CHH; known as Kallmann syndrome when it is associated with anosmia).[115] In recent years, significant advances

have been made in the identification and sequencing of genes associated with CHH, and many children with CHH can successfully achieve fertility with a combination of GnRH treatment and assisted reproductive technology.[115] Prader-Willi syndrome, in which a child carries 2 copies of the paternally imprinted chromosome 15, has also been associated with hypogonadotrophic hypogonadism and cryptorchidism.[116]

Childhood cancer survivors are at increased risk of developing hypogonadism as well as premature puberty.[117] Precocious puberty, in which the development of secondary sexual characteristics begins before 9 years old, is most common in children who received cranial irradiation at doses exceeding 18 Gy.[118,119] Central hypogonadism is more likely to develop in children who have received cranial irradiation at doses exceeding 30 Gy or who have had cranial surgery with potential damage to either the hypothalamus or the pituitary.[120–122] Primary hypogonadism in cancer survivors can develop secondary to direct chemotherapy-induced or radiation-induced toxicity; the chemotherapeutic effects do not appear to be dose-dependent, whereas those of radiation are, modified by the age of the patient (24 Gy before puberty and 30 Gy after puberty).[123–125]

SUMMARY

Fertility is an important arena for pediatric urologists, as fertility concerns impact our patients and families. Knowledge and ongoing advances in the field will greatly impact the quality of the care we deliver to our pediatric and adolescent patients as well as the quality of life for our patients across their lifetimes.

REFERENCES

1. 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.
2. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril 2008; 90:S60.
3. Zebrack BJ, Casillas J, Nohr L, et al. Fertility issues for young adult survivors of childhood cancer. Psychooncology 2004;13:689–99.
4. Hammond C, Abrams JR, Syrjala KL. Fertility and risk factors for elevated infertility concern in 10-year hematopoietic cell transplant survivors and case-matched controls. J Clin Oncol 2007;25: 3511–7.
5. Saito K, Suzuki K, Iwasaki A, et al. Sperm cryopreservation before cancer chemotherapy helps in the emotional battle against cancer. Cancer 2005; 104:521–4.
6. Schrader M, Muller M, Straub B, et al. The impact of chemotherapy on male fertility: a survey of the biologic basis and clinical aspects. Reprod Toxicol 2001;15:611–7.
7. Meistrich ML. Male gonadal toxicity. Pediatr Blood Cancer 2009;53:261–6.
8. Howell SJ, Shalet SM. Spermatogenesis after cancer treatment: damage and recovery. J Natl Cancer Inst Monogr 2005;(34):12–7.
9. Isaksson S, Bogefors K, Ståhl O, et al. High risk of hypogonadism in young male cancer survivors. Clin Endocrinol (Oxf) 2018;88:432–41.
10. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001;7:535–43.
11. Sanders JE, Hawley J, Levy W, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996;87: 3045–52.
12. Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA 1988;259:2123–5.
13. Meistrich ML, Chawla SP, Da Cunha MF, et al. Recovery of sperm production after chemotherapy for osteosarcoma. Cancer 1989;63:2115–23.
14. Averette HE, Boike GM, Jarrell MA. Effects of cancer chemotherapy on gonadal function and reproductive capacity. CA Cancer J Clin 1990;40:199–209.
15. Pryzant RM, Meistrich ML, Wilson G, et al. Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-Hodgkin's lymphomas. J Clin Oncol 1993;11:239–47.
16. Brydoy M, Fossa SD, Klepp O, et al. Paternity following treatment for testicular cancer. J Natl Cancer Inst 2005;97:1580–8.
17. 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.
18. Longhi A, Macchiagodena M, Vitali G, et al. Fertility in male patients treated with neoadjuvant chemotherapy for osteosarcoma. J Pediatr Hematol Oncol 2003;25:292–6.
19. Williams D, Crofton PM, Levitt G. Does ifosfamide affect gonadal function? Pediatr Blood Cancer 2008;50:347–51.
20. Ridola V, Fawaz O, Aubier F, et al. Testicular function of survivors of childhood cancer: a comparative study between ifosfamide- and cyclophosphamide-based regimens. Eur J Cancer 2009;45:814–8.

21. Wasilewski-Masker K, Seidel KD, Leisenring W, et al. Male infertility in long-term survivors of pediatric cancer: a report from the childhood cancer survivor study. J Cancer Surviv 2014;8:437–47.
22. Webster KE, O'Bryan MK, Fletcher S, et al. Meiotic and epigenetic defects in Dnmt3L-knockout mouse spermatogenesis. Proc Natl Acad Sci U S A 2005; 102:4068–73.
23. Yaman R, Grandjean V. Timing of entry of meiosis depends on a mark generated by DNA methyltransferase 3a in testis. Mol Reprod Dev 2006;73:390–7.
24. Hammoud SS, Purwar J, Pflueger C, et al. Alterations in sperm DNA methylation patterns at imprinted loci in two classes of infertility. Fertil Steril 2010;94:1728–33.
25. Marques CJ, Costa P, Vaz B, et al. Abnormal methylation of imprinted genes in human sperm is associated with oligozoospermia. Mol Hum Reprod 2008;14:67–74.
26. Barton TS, Robaire B, Hales BF. Epigenetic programming in the preimplantation rat embryo is disrupted by chronic paternal cyclophosphamide exposure. Proc Natl Acad Sci U S A 2005;102: 7865–70.
27. Oakes CC, Kelly TL, Robaire B, et al. Adverse effects of 5-aza-2'-deoxycytidine on spermatogenesis include reduced sperm function and selective inhibition of de novo DNA methylation. J Pharmacol Exp Ther 2007;322:1171–80.
28. Shnorhavorian M, Schwartz SM, Stansfeld B, et al. Differential DNA methylation regions in adult human sperm following adolescent chemotherapy: potential for epigenetic inheritance. PLoS One 2017;12:e0170085.
29. Schover LR. Premature ovarian failure and its consequences: vasomotor symptoms, sexuality, and fertility. J Clin Oncol 2008;26:753–8.
30. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys 2009;73:1304–12.
31. Dillon KE, Gracia CR. Pediatric and young adult patients and oncofertility. Curr Treat Options Oncol 2012;13:161–73.
32. Koch J, Ledger W. Ovarian stimulation protocols for onco-fertility patients. J Assist Reprod Genet 2013; 30:203–6.
33. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online 2009;18:769–76.
34. Dolmans MM, Marinescu C, Saussoy P, et al. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood 2010;116:2908–14.
35. Dolmans MM, Marotta ML, Pirard CL, et al. Ovarian tissue cryopreservation followed by controlled ovarian stimulation and pick-up of mature oocytes does not impair the number or quality of retrieved oocytes. J Ovarian Res 2014;7:80.
36. Lawrenz B, Rothmund R, Neunhoeffer E, et al. Fertility preservation in prepubertal girls prior to chemotherapy and radiotherapy–review of the literature. J Pediatr Adolesc Gynecol 2012;25:284–8.
37. Nahata L, Caltabellotta NM, Yeager ND, et al. Fertility perspectives and priorities among male adolescents and young adults in cancer survivorship. Pediatr Blood Cancer 2018;65(7):e27019.
38. Shnorhavorian M, Harlan LC, Smith AW, et al. Fertility preservation knowledge, counseling, and actions among adolescent and young adult patients with cancer: a population-based study. Cancer 2015;121:3499–506.
39. Wallace WH. Fertility preservation for young people treated with cancer: what are the attitudes and knowledge of clinicians. Pediatr Blood Cancer 2007;48:2–3.
40. 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.
41. 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.
42. Shnorhavorian M, Kroon L, Jeffries H, et al. Creating a standardized process to offer the standard of care: continuous process improvement methodology is associated with increased rates of sperm cryopreservation among adolescent and young adult males with cancer. J Pediatr Hematol Oncol 2012;34:e315–9.
43. Ginsberg JP, Li Y, Carlson CA, et al. Testicular tissue cryopreservation in prepubertal male children: an analysis of parental decision-making. Pediatr Blood Cancer 2014;61:1673–8.
44. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31:2500–10.
45. Hudson J, Vadaparampil ST, Tamargo C, et al. Fertility preservation in cancer patients with a poor prognosis: the controversy of posthumous reproduction. Future Oncol 2016;12:1675–7.
46. Claahsen-van der Grinten HL, Stikkelbroeck NMML, Sweep CG, et al. Fertility in patients with congenital adrenal hyperplasia. J Pediatr Endocrinol Metab 2006;19:677–85.
47. Nebesio TD, Eugster EA. Growth and reproductive outcomes in congenital adrenal hyperplasia. Int J Pediatr Endocrinol 2010;2010:298937.
48. Conway GS, Casteras A, De Silva P, et al. Reassessing fecundity in women with classical congenital adrenal hyperplasia (CAH): normal pregnancy

rate but reduced fertility rates. Clin Endocrinol 2009;70:833–7.
49. Bidet M, Bellanne-Chantelot C, Galand-Portier MB, et al. Fertility in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab 2010;95:1182–90.
50. Sahakitrungruang T. Clinical and molecular review of atypical congenital adrenal hyperplasia. Ann Pediatr Endocrinol Metab 2015;20:1–7.
51. Burckhardt MA, Udhane SS, Marti N, et al. Human 3-beta-hydroxysteroid dehydrogenase deficiency seems to affect fertility but may not harbor a tumor risk: lesson from an experiment in nature. Eur J Endocrinol 2015;173:K1–12.
52. Fukami M, Tsutomu O. Cytochrome P450 oxidoreductase deficiency: rare congenital disorder leading to skeletal malformations and steroidogenic defects. Pediatr Int 2014;56:805–8.
53. Diamond DA, Yu RN. Disorders of sexual development: etiology, evaluation, and medical management. In: Wein AJ, Kavoussi LR, Partin AW, et al, editors. Campbell-Walsh urology. 11th edition. Philadelphia: Elsevier; 2016. p. 3469–97.
54. Guercio G, Costanzo M, Grinspon RP, et al. Fertility issues in disorders of sex development. Endocrinol Metab Clin North Am 2015;44:867–81.
55. 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.
56. Rutgers JL, Scully RE. The androgen insensitivity syndrome (testicular feminization): a clinicopathologic study of 43 cases. Int J Gynecol Pathol 1991;10:126–44.
57. Kang HJ, Imperato-McGinley J, Zhu YS, et al. 5-alpha- reductase-2 deficiency's effect on human fertility. Fertil Steril 2014;101:310–6.
58. Wisniewski AB, Hiort O, Holterhus PM. Androgen insensitivity and male infertility. Int J Androl 2003; 26:16–20.
59. Mazur T. 46,XY DSD with female or ambiguous external genitalia at birth due to androgen insensitivity syndrome, 5alpha-reductase-2 deficiency, or 17beta-hydroxysteroid dehydrogenase deficiency: a review of quality of life outcomes. Int J Pediatr Endocrinol 2009;2009:567430.
60. Cools M, Drop SL, Wolffenbuttel KP, et al. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev 2006;27: 468–84.
61. Schultz BAH, Roberts S, Rodgers A, et al. Pregnancy in true hermaphrodites and all male offspring to date. Obstet Gynecol 2009;113:534–6.
62. Sugawara N, Kimura Y, Araki Y. A successful second delivery outcome using refrozen thawed testicular sperm from an infertile male true hermaphrodite with a 46,XX/46,XY karyotype: case report. Hum Cell 2012;25:96–9.
63. Vorona E, Zitzmann M, Gromoll J, et al. Clinical, endocrinological, and epigenetic features of the 46,XX male syndrome, compared with 47,XXY Klinefelter patients. J Clin Endocrinol Metab 2007; 92:3458–65.
64. Wattendorf DJ, Muenke M. Klinefelter's syndrome. Am Fam Physician 2005;72:2259–62.
65. Aksglaede L, Wikström AM, Rajpert-De Meyts E, et al. Natural history of seminiferous tubule degeneration in Klinefelter syndrome. Hum Reprod Update 2006;12:39–48.
66. Franik S, Hoeijmakers Y, D'Hauwers K, et al. Klinefelter syndrome and fertility: sperm preservation should not be offered to children with Klinefelter syndrome. Hum Reprod 2016;31:1952–9.
67. Gies I, Oates R, De Schepper J, et al. Testicular biopsy and cryopreservation for fertility preservation of prepubertal boys with Klinefelter syndrome: a pro/con debate. Fertil Steril 2016;105:249–55.
68. Hovatta O. Pregnancies in women with Turner's syndrome. Ann Med 1999;31:106–10.
69. Karnis MF. Fertility, pregnancy, and medical management of Turner syndrome in the reproductive years. Fertil Steril 2012;98:787–91.
70. Johansen ML, Hagen CP, Rajpert-De Meyts E, et al. 45,X/46,XY mosaicism: phenotypic characteristics, growth, and reproductive function e a retrospective longitudinal study. J Clin Endocrinol Metab 2012; 97:E1540–9.
71. Martinerie L, Morel Y, Gay CL, et al. Impaired puberty, fertility, and final stature in 45,X/46,XY mixed gonadal dysgenetic patients raised as boys. Eur J Endocrinol 2012;166:687–94.
72. Finlayson C, Johnson EK, Chen D, et al. Proceedings of the working group session on fertility preservation for individuals with gender and sex diversity. Transgend Health 2016;1:99–107.
73. Chen D, Matson M, Macapagal K, et al. Attitudes toward fertility and reproductive health among transgender and gender-nonconforming adolescents. J Adolesc Health 2018 [pii:S1054-S1139X(17)30908-4].
74. Strang JF, Jarin J, Call D, et al. Transgender youth fertility attitudes questionnaire: measure development in nonautistic and autistic transgender youth and their parents. J Adolesc Health 2017;62: 128–35.
75. Chen D, Simons L, Johnson EK, et al. Fertility preservation for transgender adolescents. J Adolesc Health 2017;61:120–3.
76. De Roo C, Lierman S, Tilleman K, et al. Ovarian tissue cryopreservation in female-to-male transgender people: insights into ovarian histology and physiology after prolonged androgen treatment. Reprod Biomed Online 2017;34:557–66.

77. Eckersten D, Giwercman A, Pihlsgård M, et al. Impact of kidney transplantation on reproductive hormone levels in males: a longitudinal study. Nephron 2018;138:192–201.
78. Sarkar M, Bramham K, Moritz M, et al. Reproductive health in women following abdominal organ transplant. Am J Transplant 2018;18(5):1068–76.
79. de Jong PH, Dolhain RJ. Fertility, pregnancy, and lactation in rheumatoid arthritis. Rheum Dis Clin North Am 2017;43:227–37.
80. Micu MC, Ostensen M, Villiger PM, et al. Paternal exposure to antirheumatic drugs—What physicians should know: review of the literature. Semin Arthritis Rheum 2018 [pii:S0049-0172(17)30747-3].
81. Brouwer J, Hazes JM, Laven JS, et al. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis 2015;74:1836–41.
82. Provost M, Eaton JL, Clowse ME. Fertility and infertility in rheumatoid arthritis. Curr Opin Rheumatol 2014;26:308–14.
83. Brouwer J, Laven JS, Hazes JM, et al. Levels of serum anti-Mullerian hormone, a marker for ovarian reserve, in women with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013;65:1534–8.
84. Henes M, Froeschlin J, Taran FA, et al. Ovarian reserve alterations in premenopausal women with chronic inflammatory rheumatic diseases: impact of rheumatoid arthritis, Behcet's disease and spondyloarthritis on anti-Mullerian hormone levels. Rheumatology (Oxford) 2015;54:1709–12.
85. Martini AC, Molina RI, Tissera AD, et al. Analysis of semen from patients chronically treated with low or moderate doses of aspirin-like drugs. Fertil Steril 2003;80:221–2.
86. Østensen M. Sexual and reproductive health in rheumatic disease. Nat Rev Rheumatol 2017;13:485–93.
87. Kokoszko-Bilska A, Sobkiewicz S, Fichna J. Inflammatory bowel diseases and reproductive health. Pharmacol Rep 2016;68:859–64.
88. Dejaco C, Mittermaier C, Reinisch W, et al. Azathioprine treatment and male fertility in inflammatory bowel disease. Gastroenterology 2001;121:1048–53.
89. Massenkeil G, Alexander T, Rosen O, et al. Long-term follow-up of fertility and pregnancy in autoimmune diseases after autologous haematopoietic stem cell transplantation. Rheumatol Int 2016;36:1563–8.
90. Nahata L, Sivaraman V, Quinn GP. Fertility counseling and preservation practices in youth with lupus and vasculitis undergoing gonadotoxic therapy. Fertil Steril 2016;106:1470–4.
91. Akbay E, Cayan S, Doruk E, et al. The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. BJU Int 2000;86:490–3.
92. Meacham RB, Townsend RR, Rademacher D, et al. The incidence of varicoceles in the general population when evaluated by physical examination, gray scale sonography and color Doppler sonography. J Urol 1994;151:1535–8.
93. Bertolla RP, Cedenho AP, Hassun Filho PA, et al. Sperm nuclear DNA fragmentation in adolescents with varicocele. Fertil Steril 2006;85:625–8.
94. Lacerda JI, Del Giudice PT, da Silva BF, et al. Adolescent varicocele: improved sperm function after varicocelectomy. Fertil Steril 2011;95:994–9.
95. Locke JA, Noparast M, Afshar K. Treatment of varicocele in children and adolescents: a systematic review and meta-analysis of randomized controlled trials. J Pediatr Urol 2017;13:437–45.
96. Fine RG, Gitlin J, Reda EF, et al. Barriers to use of semen analysis in the adolescent with a varicocele: survey of patient, parental, and practitioner attitudes. J Pediatr Urol 2016;12:e1–6.
97. Nork JJ, Berger JH, Crain DS, et al. Youth varicocele and varicocele treatment: a meta-analysis of semen outcomes. Fertil Steril 2014;102:381–7.
98. Li F, Chiba K, Yamaguchi K, et al. Effect of varicocelectomy on testicular volume in children and adolescents: a meta-analysis. Urology 2012;79:1340–5.
99. Keene DJ, Fitzgerald CT, Cervellione RM. Sperm concentration and forward motility are not correlated with age in adolescents with an idiopathic varicocele and symmetrical testicular volumes. J Pediatr Surg 2016;51:293–5.
100. Alkaram A, McCullough A. Varicocele and its effect on testosterone: implications for the adolescent. Transl Androl Urol 2014;3:413–7.
101. Li F, Yue H, Yamaguchi K, et al. Effect of surgical repair on testosterone production in infertile men with varicocele: a meta-analysis. Int J Urol 2012;19:149–54.
102. Damsgaard J, Joensen UN, Carlsen E, et al. Varicocele is associated with impaired semen quality and reproductive hormone levels: a study of 7035 healthy young men from six European countries. Eur Urol 2016;70:1019–29.
103. Cayan S, Şahin S, Akbay E. Paternity rates and time to conception in adolescents with varicocele undergoing microsurgical varicocele repair vs observation only: a single institution experience with 408 patients. J Urol 2017;198:195–201.
104. Cortes D, Kjellberg EM, Breddam M, et al. The true incidence of cryptorchidism in Denmark. J Urol 2008;179:314–8.
105. Nah SA, Yeo CS, How GY, et al. Undescended testis: 513 patients' characteristics, age at orchidopexy and patterns of referral. Arch Dis Child 2014;99:401–6.
106. Noh PH, Cooper CS, Snyder HM 3rd, et al. Testicular volume does not predict germ cell count in patients with cryptorchidism. J Urol 2000;163:593–6.

107. Hadziselimovic F, Thommen L, Girard J, et al. The significance of postnatal gonadotropin surge for testicular development in normal and cryptorchid testes. J Urol 1986;136:274–6.
108. Kolon TF, Herndon CDA, Baker LA, et al. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014;192:337–45.
109. Rohayem J, Luberto A, Nieschlag E, et al. Delayed treatment of undescended testes may promote hypogonadism and infertility. Endocrine 2017;55:914–24.
110. Pacilli M, Heloury Y, O'Brien M, et al. Orchidopexy in children with Prader-Willi syndrome: results of a long-term follow-up study. J Pediatr Urol 2018;14:e1–6.
111. Hadziselimovic F, Gegenschatz-Schmid K, Verkauskas G, et al. GnRHa treatment of cryptorchid boys affects genes involved in hormonal control of the HPG axis and fertility. Sex Dev 2017;11:126–36.
112. Kraft KH, Canning DA, Snyder HM 3rd, et al. Undescended testis histology correlation with adult hormone levels and semen analysis. J Urol 2012;188:1429–35.
113. Dohle GR, Arver S, Bertocchi C, et al. EAU guidelines on male hypogonadism. 2016. Available at: http://www.uroweb.org/guidelines/online-guidelines/. Accessed April 1, 2018.
114. Howell SJ, Radford JA, Adams JE, et al. The impact of mild Leydig cell dysfunction following cytotoxic chemotherapy on bone mineral density (BMD) and body composition. Clin Endocrinol (Oxf) 2000;52:609–16.
115. Maione L, Dwyer AA, Francou B, et al. Genetics in endocrinology: genetic counseling for congenital hypogonadotropic hypogonadism and Kallmann syndrome: new challenges in the era of oligogenism and next-generation sequencing. Eur J Endocrinol 2018;178:R55–80.
116. Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 2017. p. 1993–2018.
117. Kenney LB, Cohen LE, Shnorhavorian M, et al. Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. J Clin Oncol 2012;30:3408–16.
118. Oberfield SE, Soranno D, Nirenberg A, et al. Age at onset of puberty following high-dose central nervous system radiation therapy. Arch Pediatr Adolesc Med 1996;150:589–92.
119. Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. J Clin Endocrinol Metab 1994;78:1282–6.
120. Romerius P, Stahl O, Moell C, et al. Hypogonadism risk in men treated for childhood cancer. J Clin Endocrinol Metab 2009;94:4180–6.
121. Livesey EA, Hindmarsh PC, Brook CG, et al. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 1990;61:622–5.
122. Darzy KH, Shalet SM. Hypopituitarism following radiotherapy revisited. Endocr Dev 2009;15:1–24.
123. Izard MA. Leydig cell function and radiation: a review of the literature. Radiother Oncol 1995;34:1–8.
124. Shalet SM, Horner A, Ahmed SR, et al. Leydig cell damage after testicular irradiation for lymphoblastic leukaemia. Med Pediatr Oncol 1985;13:65–8.
125. Blatt J, Sherins RJ, Niebrugge D, et al. Leydig cell function in boys following treatment for testicular relapse of acute lymphoblastic leukemia. J Clin Oncol 1985;3:1227–31.