Detection and Management Of Pediatric Conditions that May Affect Male Fertility

Geolani W. Dy, Melissa Rust, and Pamela Ellsworth

Couple infertility is related to male factors in 50% of cases (Jungwirth et al., 2012). In adult males, the cause often relates to obstruction of the male genital tract or decreased or absent sperm production or function. While the vast majority of infertility evaluations are performed for adults, several conditions affecting male fertility may be detected in childhood, including congenital, structural, and traumatic etiologies (see Table 1).

**Pediatric Diagnoses Contributing To Infertility**

An understanding of pediatric diagnoses contributing to infertility can facilitate management plans, and the impact of these diagnoses should be discussed with patients and their parents in preparation for postpubertal years. When a child or adolescent is diagnosed with a condition that may affect future fertility, it is often met with great anxiety by the parents and patient. At the time of diagnosis, about 30% of adolescents experience anxiety and depressed mood related to the diagnosis (Steeno, Knops, Declerck, Adimoelja, & van de Voorde, 1976). Likewise,
parents may be concerned about potential fertility issues related to these diagnoses. Urology nurses and midlevel providers are helpful in recognizing such concerns, serving as a health information resource to facilitate patient and family understanding of the diagnosis and relieving some anxiety. The prevalence rates, pathophysiology, current evaluation, and management options of the most commonly encountered pediatric causes of male infertility are discussed.

History

The pediatric history focuses on prenatal history, including prenatal ultrasound-detected genital anomalies, in utero exposures, and the mother’s prenatal course.

The postnatal history includes developmental, medical, and surgical history, as well as the presence or absence of physical abnormalities on initial examination.

Social history and identification of substance abuse is especially important in adolescent patients. Anabolic steroid abuse and chronic opioid use are more common in this population and may cause hypogonadism through dysregulation of normal gonadotrophic pathways (Jarow & Lipshultz, 1990; Vuong, Van Uum, O’Dell, Lufty, & Friedman, 2010). Providers need to be perceptive at identifying risk factors for use of these substances and educate about potential long-term effects on fertility.

Initial Evaluation and Physical Examination

Many stigmata of infertility can be found on careful physical examination, with an emphasis on the genital examination, which is especially important in the prepubertal population. Male genital development assessment includes penile size, urethral meatal location, testis size, and location in all males regardless of age. In the post-pubertal male, manifestations of hypogonadism may include underdeveloped secondary sexual characteristics, decreased male pattern hair distribution (axillary, body, facial, pubic), gynecomastia, and eunuchoid body habitus (arm span 5 cm or more greater than height). The Tanner scale (see Table 2) is used to assess sexual development, and in males, to assess pubic hair and genitalia, including scrotal development, testicular volume, and penile length.

Testis size should be compared to norms for the patient’s age and general chronological development. Testicular volume can be measured using a simple ruler, an orchidometer, comparative ovoids, or in select cases, ultrasonography (Taskinen, Taavitsainen, & Wikstrom, 1996). Assessment for a varicocele should occur while lying, standing, and with

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<th>Chromosomal</th>
<th>Structural</th>
<th>Metabolic</th>
<th>Illicit Drug Use</th>
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<td>Klinefelter syndrome</td>
<td>Varicocele</td>
<td>Growth hormone deficiency</td>
<td>Marijuana, cocaine, smoking</td>
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<td>Noonan syndrome</td>
<td>Undescended testes</td>
<td>Panhypopituitarism</td>
<td>Anabolic steroid abuse</td>
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Table 1. Common Pediatric Factors Affecting Male Fertility

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<tr>
<th>Stage</th>
<th>Pubic Hair</th>
<th>Genitalia</th>
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<tr>
<td>Stage I</td>
<td>No pubic hair</td>
<td>Testes less than 2.5 cm, small penis of 3 cm or less</td>
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<td>Stage II</td>
<td>Small amount of long, downy hair with slight pigmentation at base of penis and scrotum</td>
<td>Testis volume between 2.5 to 3.2 cm; skin on scrotum thins, reddens, and enlarges; penis unchanged</td>
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<td>Stage III</td>
<td>Hair becomes coarse and curly and begins to extend laterally</td>
<td>Testis volume between 3.3 and 4.0 cm, scrotum enlarges further, penis increases in length to about 6 cm</td>
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<tr>
<td>Stage IV</td>
<td>Adult-like hair quality, extending across pubis, sparing medial thighs</td>
<td>Testis volume 4.1 to 4.5 cm, scrotum enlarges further and darkens, penis increases in length to 10 cm and increases in circumference</td>
</tr>
<tr>
<td>Stage V</td>
<td>Adult-like quality, extending across pubis and medial thighs</td>
<td>Volume greater than 4.5 cm, adult scrotum and penis of 15 cm in length</td>
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Sources: Blondell, Foster, & Dave, 1999; Tanner & Tanner, 1970.
Valsalva maneuver. Although rare in prepubertal males, varicoceles (see Figure 1) may occur, and it is recommended that prepubertal males be examined in the standing position because the varicoceles tend to be Grade II or less (Vasavada, Ross, Nasrallah, & Kay, 1997). Although more difficult than in the adult population, careful examination may allow for detection of absence of the vas deferens in the prepubertal or adolescent male. Epididymal anomalies may be more difficult to identify.

Semen analyses are a cornerstone of the adult infertility evaluation but have limited availability for pediatric patients. The ability to obtain a semen analysis is dependent on patient maturity, as well as parent and physician level of comfort. In the adolescent male with a varicocele, serial measurement of testicular volume is thought to be useful in determining whether or not the varicocele is having an adverse effect on testicular function (Barthold, 2011). However, there is controversy as to the correlation between testicular volume and semen analysis.

Haans, Laven, Mali, te Velde, and Wensing (1991) noted that left testicular growth failure in adolescents with a varicocele was only associated with a decrease in total sperm number, whereas Guarino, Tadini, and Bianchi (2003) concluded that the evaluation of testicular volumes during examination for varicocele in Tanner Stage V adolescents is not predictive for testicular dysfunction.

Laboratory studies often include semen analysis when acceptable, endocrine evaluation, and genetic testing. The American Urological Association (AUA) (2010) best practice guidelines on the optimal evaluation of the infertile male recommend that at least two semen analyses be obtained after a defined period of abstinence of two to three days. If the specimen is being collected through the use of a condom, it is important the condom does not contain substances that would be detrimental to sperm. In addition, the collection container should be kept at room or body temperature and should be examined within one hour of collection. The semen volume and concentration should be noted in addition to sperm morphology, motility, and progression.

Ultrasound, frequently utilized in the pediatric urologic evaluation, can be used for measuring testis size, assessing subclinical varicocele presence, and measuring testicular blood flow. Other components of the laboratory and imaging workup are discussed in detail under specific diagnoses.

Congenital/Chromosomal Abnormalities

Chromosomal causes of male infertility include Klinefelter syndrome, cystic fibrosis and its variants, trisomy, Y-chromosome microdeletions, Noonan syndrome, and Kallman’s syndrome. Y-chromosome microdeletions are thought to be the most common genetic cause of azoospermia (Sadeghi-Nejad & Farrokhi, 2007). Noonan syndrome, sometimes called “male Turner’s syndrome,” is a relatively common autosomal dominant condition associated with bilateral undescended testes (UDT) (Elsawi, Pryor, Klufio, Barnes, & Patton, 1994). Kallman’s syndrome, an X-linked disorder, typically presents with facial and renal abnormalities with UDT apparent at birth.

Klinefelter Syndrome

Klinefelter syndrome is the most common sex chromosome disorder causing azoospermia (overall incidence 1:500 males) (Lanefranco, Kamischke, Zitzmann, & Nieschlag, 2004), and it is characterized by hypogonadism and infertility. The most common chromosome complement is 47, XXY. In addition, a variety of mosaic complements are possible and contribute to the variable presentation of Klinefelter syndrome, though the mosaic most frequently found is 46,XY/47, XXY. While only 10% of men with Klinefelter syndrome are di-
agnosed before puberty (Bojesen, Juul, & Grayholt, 2003), new advancements in fertility preservation have made this a period of interest for investigation and possible initiation of treatment. Some children may be diagnosed prenatally, and subtle age-related clinical findings may prompt chromosomal evaluation in the infant or child. Such clinical signs include 1) infants with hypospadias, small phallus, cryptorchidism, or developmental delay; 2) kindergarten-aged boys and elementary school-aged boys with developmental delay, learning disabilities, or behavioral problems; and 3) older boys and adolescent males with eunuchoid body habitus, gynecomastia, or small testes (Radicioni et al., 2010; Ross et al., 2005; Visootsak & Graham, 2006).

**Physical findings.** The classic triad of Klinefelter syndrome includes small firm testes, azoospermia, and gynecomastia in an adult male. The physiologically smaller prepubertal testis makes abnormality more difficult to discern, but testes volume less than 1.5 mL indicates loss of germ cells before puberty and should lead clinics to perform cytogenetic evaluation (Paduch, Bolyakov, Cohen, & Travis, 2009). Historically, patients with Klinefelter syndrome have been described to exhibit delayed sexual maturation, increased height with exaggerated growth of lower extremities, decreased strength and facial hair growth, and mild to moderate cognitive impairment. It is now apparent that men with Klinefelter syndrome represent a variety of phenotypes and may only have impaired fertility, contributing to underdiagnosis of Klinefelter syndrome. The more specific findings of small testes at 5 to 7 mL (normal 12 to 30 mL) and low testosterone in postpubertal males should always prompt cytogenetic evaluation.

**Laboratory evaluation.** Patients with Klinefelter syndrome tend to have a pattern of primary testicular failure, such as low to low-normal testosterone and elevated luteinizing hormone (LH), follicular stimulating hormone (FSH), and serum estradiol. Hormonal evaluation may also include prolactin, insulin-like growth factor-1 (IGF-1), and cortisol due to increasing evidence of adrenal steroidogenic deficiency in Klinefelter syndrome (Paduch et al., 2009). Peripheral blood cytogenetics are usually adequate for diagnosis, although mosaicism less than 10% may not be detected. The gold standard for postnatal diagnosis is karyotyping, but if unavailable, fluorescence in situ hybridization (FISH) and molecular techniques have been used. An optimal diagnostic test for Klinefelter syndrome would allow for screening at birth of groups at higher risk for nondisjunction – children born from older parents (Lorda-Sanchez, Binkert, Maechler, Robinson, & Schinzell, 1992) or through assisted reproductive technology (ART) (Aboulghar et al., 2001).

**Fertility preservation.** Treatment options in adolescents and adults differ, especially in younger adolescents. Fertility preservation should be discussed with both the teen and his parents. The loss of spermatogonial cells in males with Klinefelter syndrome appears to occur progressively, and most boys are born with spermatogonia that undergo massive apoptosis most likely during early puberty (Lin, Huang, Lin, & Kup, 2004; Wikstrom et al., 2004; Yamamoto et al., 2002). It appears there is a period in early puberty when spermatogenesis begins and sperm are present in the ejaculate. This time frame presents an opportunity to obtain ejaculated sperm or sperm from testicular biopsy for cryopreservation. This is controversial. Although Wikstrom and colleagues (2004) found that apoptosis of spermatogonia occurs in the testes of men with Klinefelter syndrome at the onset of puberty, they also concluded that early puberty does not provide a unique window for increasing fertility potential of patients with Klinefelter syndrome because testicular germ cells of these patients show a maturational arrest and no meiotic cells on biopsy.

At present, it is recommended that fertility preservation in adolescents be performed at skilled centers because the team needs to address complex ethical, legal, and logistic issues that arise when a child with a genetic defect is being subjected to interventions. Benefits of these interventions, although likely, are not certain at this point in time (Paduch et al., 2009).

Prospective studies evaluating the use of aromatase inhibitors in adolescents with Klinefelter syndrome are ongoing; however, more data are needed before widespread use can be adopted. Aromatase inhibitors, such as anastrozole (Arimidex®), have been used off-label to decrease intratesticular estradiol and increase testosterone production, and are thought to offer a physiologic treatment for Klinefelter syndrome (Paduch et al., 2009).

Testosterone replacement has been a mainstay of Klinefelter syndrome treatment, and is successful in correcting androgen deficiency symptoms but inadequate for improving infertility. More recently, testicular sperm extraction (TESE) and use of this sperm for in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have resulted in successful pregnancies from men with Klinefelter syndrome (Palermo et al., 1998).

A limitation of fertility preservation in such males is the lack of a recognized and well-accepted set of markers, which would allow one to determine the best timing for cryopreservation. Paduch and colleagues (2009) recommend monitoring adolescents with Klinefelter syn-
drome with FSH, LH, testosterone, inhibin B, and testicular volume measurements every six months, starting two years before predicted onset of puberty. Morning urine samples from two consecutive days are obtained, spun, and evaluated for the presence of sperm. Physical examination, including assessment of testicular volume, is performed every six months. When the FSH and LH start to increase, a discussion is held with the parents to determine the best method of sperm retrieval. If the child is comfortable with masturbation – typically around 12 years of age in the American Caucasian population (Kinsey, Pomeroy, & Martin, 2003) – a semen sample can be collected and evaluated for sperm. If sperm are found, anastrozole is administered for six months, and additional semen specimens are obtained and cryopreserved. If no sperm are found but the FSH continues to increase, the microsurgical testicular sperm retrieval is offered with cryopreservation if sperm are identified (Paduch et al., 2009).

**Congenital Bilateral Absence of the Vas Deferens and Cystic Fibrosis**

Absence of all or a portion of the vas deferens may indicate the presence of cystic fibrosis or variants. Patients with cystic fibrosis can have bilateral absence of the vas deferens (CBAVD) or unilateral absence of the vas deferens (CUAVD) with a normal or obstructed contralateral vas deferens. This may be associated with partial or complete agenesis of the epididymis and seminal vesicles. Cystic fibrosis is the most common autosomal recessive genetic disorder in the United States and is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR mutations are more common in males with CBAVD (Casals et al., 2000). With severe CFTR mutations, cystic fibrosis presents in full form with fluid and electrolyte abnormalities, chronic lung obstruction and infection, and pancreatic insufficiency. Infertility is due to missing portions of the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts, leading to obstructive azoospermia. A phenotype of isolated CBAVD and infertility occurs with a different spectrum or alternatively spliced mutations of CFTR genes (Cuppens & Cassiman, 2004). Spermatogenensis in these patients is normal, and infertility is the result of obstruction. On physical examination, there is no palpable vas deferens bilaterally.

**Screening for cystic fibrosis.** Most states routinely screen all Caucasian newborns, the group with highest incidence of cystic fibrosis, which has led to better nutritional and pulmonary outcomes (Southern, Mérelle, Dankert-Roele, & Nagelkerke, 2009). Recently, it has been suggested that community-tailored cystic fibrosis screening panels may benefit individuals from other ethnic groups who may carry different mutations (Comeau et al., 2007). The newborn screening test does not actually diagnose cystic fibrosis; if the results are abnormal, further tests, including a sweat test and genetic testing, can be performed. However, there have been reports of absence of the vas deferens as the first sign of the diagnosis of cystic fibrosis in infants, and less severe CFTR mutations may only be detected in the infertility evaluation of men with obstructive azoospermia, especially prior to ICSI (Mocanu et al., 2010).

One classic sign of cystic fibrosis is an excessively salty taste to the child’s skin, which parents may taste when they kiss their child. Other signs and symptoms include persistent cough, wheezing, repeated pulmonary and sinus infections, foul-smelling greasy stools, poor weight gain and growth, distended abdomen and constipation, and intestinal obstruction, particularly in newborns (Egan, 2011).

**Genetic counseling.** Male patients positive for CFTR mutations should undergo genetic counseling, and their female partners should also be screened to rule out carrier status.

**Structural Anomalies**

**Varicocele**

Approximately 30% to 50% of males with infertility have varicocele (Jarow, Coburn, & Sigman, 1996; Nashan, Behre, Grünert, & Nieschlag, 1990; Opitz, Shapiro, & Uehling, 1979). Varicocele is more common on the left than right. Although more commonly identified in adolescence, varicocele can occasionally be noted in pre-adolescent boys (Buch & Cromie, 1985; Saeczuk, Hensle, Burbige, & Nagler, 1993). In older adolescents, the reported incidence ranges from 12.4% to 17.8%, which is similar to that in adult males (Paduch & Skoog, 2001). The abnormal dilatation of the pampiniform plexus and internal spermatic vein often arises in puberty, when increased testicular blood flow exposes underlying anatomic abnormalities, such as faulty valvular venous return, venous collaterals, and increased venous pressure.

**Evaluation.** Patients may complain of scrotal discomfort or “heaviness,” but more often, varicoceles are found on routine physical examination. Diagnosis and management of varicoceles depend heavily on physical findings, although various imaging modalities may be used as confirmation.

The patient should be examined in a warm room for a pos tersuperior scrotal bulge while laying and standing. The standing patient should also be evaluated during a Valsalva maneuver, which may accentuate smaller varicoceles. Grading is subjective and based on examination.
Subclinical varicoceles are non-palpable but detectable with ultrasound or venography; Grade I varicoceles are small and palpable upon Valsalva; Grade II varicoceles are moderate and palpable without maneuvers; and Grade III varicoceles are large and visible from a distance. Varicoceles that are acute in onset, appear prior to puberty, do not reduce on supine examination, and/or are present on the right side should raise suspicion for an obstructing retroperitoneal mass.

When following a child with a varicocele, it is important that the same provider use the same tool to assess testicular size/volume consistently to minimize variation in measurements. In most males, the initial volume determination will serve as a comparator for future examinations. However, if a significant size discrepancy between the affected and normal contralateral testis is noted, it may dictate therapy.

**Impact on fertility.** Numerous studies have shown a definite association between varicocele and male infertility, although a direct cause-and-effect relationship has not been conclusively established (Zini & Boman, 2009). Many theories exist regarding the impact of varicocele on fertility, including hyperthermia, hypoxia, hyperperfusion injury, increased reactive oxygen species, and reflux of renal or adrenal metabolites. Effects on the testis include growth failure of the ipsilateral testes, decreased spermatogenesis, semen abnormalities, Leydig cell dysfunction and atrophy, and histologic changes, such as tubular thickening.

**Determining Who to Treat**

The correlation between varicocele grade and testicular size, semen analysis, and fertility remains controversial in adults and children (Lyon, Marschall, & Scott, 1983; Paduch & Niedzielski, 1997; Sigman & Jarow, 1997; Vereecken & Boeckx, 1986). Lyon et al. (1983) found no correlation between varicocele grade and testicular size in 30 adolescents, whereas other researchers (Costabile, Skoog, & Radowich, 1992; Paduch & Niedzielski, 1997; Steeno et al., 1976) all independently noted that boys with severe varicocele had a smaller ipsilateral testis. Varicocele size, however, should not be used as the sole indication for varicocele treatment. Diamond and colleagues (2007) examined the relationship of varicocele grade and testicular hypotrophy to adolescent semen parameters, finding that volume differentials greater than 10% between normal and affected testes correlated with significantly reduced sperm concentration and total motile sperm count, while varicocele grade had no significant impact on semen analysis. Varicocele repair in the adolescent male with ipsilateral hypotrophy has been demonstrated to result in catch-up testicular growth in 80% (Kass & Belman, 1987).

**Management.** The presence of a varicocele in a child warrants continuous surveillance, although the ideal clinical follow-up protocol and surgical approach continue to be debated. Gargollo and Diamond (2009) recommend that adolescent patients with a varicocele be followed annually with physical examination, testicular ultrasound, and if Tanner Stage V semen analysis. In the absence of testicular disproportion or symptoms, and with normal semen analysis, patients may be followed conservatively.

Recommendations vary as to what constitutes a significant size discrepancy justifying surgical correction. If serial evaluations demonstrate decreasing ipsilateral testicular size or 20% size differential consistently over one year, surgical management should be considered. Skoog, Roberts, Goldstein, and Pryor (1997) note that a size variation of more than 2 mL by ultrasound is currently the best indicator of testicular damage in the absence of a semen analysis and serves as the minimal requirement for surgical repair of the adolescent varicocele. Not every boy with a varicocele and testicular growth arrest will be infertile. A semen analysis remains the gold standard (Paduch & Skoog, 2001).

**Undescended Testes**

Cryptorchidism (often used interchangeably with undescended testes [UDT]) affects 3% to 5% of male newborns and is the most frequent congenital abnormality of male genitalia, encompassing undescended, atrophic, and ectopic testes (Scorer & Farrington, 1971). By 1 year of age, 75% of full-term infants and 95% of premature infants with UDTs experience spontaneous descent of the testes (Berkowitz et al., 1993), and the incidence of UDT beyond 1 year of age decreases to 0.8%. Testes that remain undescended have an increased risk of infertility and malignancy; testicular cancer risk is 5 to 10 times normal (Pettersson, Richiardi, Nordenskjold, Kaijser, & Akre, 2007) and may be associated with higher rates of torsion, hernias, and anomalies of the testis and epididymis.

The etiology of UDT is presumed to be multifactorial with genetic and environmental components, but exact pathways have yet to be defined (Barthold, 2008). Premature newborns with a low birthweight, are small for gestational age, and are twins have increased incidence of cryptorchidism.

**Evaluation.** Testicular examination of the child with UDT should involve one hand on the abdomen starting at the level of the internal ring and “milking” the testis down to the external ring, and the other hand attempting to feel for the testis, distinguishing between palpable and nonpalpable testes. A palpable testis may be found along the normal pathway of descent from the internal inguinal ring toward external inguinal ring or outside.
of the normal path of testicular descent. Palpable testes outside of the scrotum can be categorized as retractile (not truly undescended), incompletely descended (within or just outside the inguinal canal), or ectopic (following a different line of descent). A nonpalpable testis is generally intra-abdominal, beneath the external oblique, or atrophic and absent (usually as a result of neonatal torsion).

Bilateral nonpalpable testes should be followed with chromosome and hormonal analysis to rule out disorders of sexual differentiation. Endocrine evaluation includes FSH, LH, testosterone, and human chorionic gonadotropin (hCG) stimulation testing, with a failure to respond to hCG stimulation indicating atrophy or anorchia. An increase in testosterone in response to stimulation suggests the presence of at least one functioning testis (Davenport et al., 1995). The hCG stimulation test and other testis hormone markers can be useful in confirming bilateral anorchia after intraoperative diagnosis or for assuring completeness of gonadectomy after surgery to avoid malignant degeneration of residual tissue (McEachern, Houle, Garel, & Van Vliet, 2004).

Imaging is not traditionally used for evaluation of nonpalpable UDT in young males. Ultrasound does not reliably localize nonpalpable testes and does not rule out the presence of an intra-abdominal testis (Tasian & Copp, 2011). However, the authors have found that with overweight prepubertal and pubertal males with a normal size contralateral testis, it may be useful in detecting a testis within the inguinal region, which is not palpable due to the large amount of adipose tissue (Ellsworth & Cheuck, 2009).

**Impact on fertility.** The effect of unilateral UDT on fertility and paternity has been debated—some studies conclude that there is minimal to no change in the likelihood of paternity, while others accept that the likelihood of paternity of a boy with unilateral descended testes decreases to two-thirds (Lee et al., 1997; Miller, Coughlin, & Lee, 2001). Semen analyses in men with untreated unilateral cryptorchidism show azoospermia or oligospermia in 50% to 70%. Bilateral UDT correspond to a marked decrease in paternity rates, estimated at one-third of the normal rate (Lee et al., 1997). The risk of infertility increases with the more abnormal the location of the testis, with an intraabdominal location having the greatest risk.

A variety of factors may result in infertility related to cryptorchidism. For the testis to produce viable sperm, the local environment must be 1.5 to 2 degrees C cooler than body temperature. The effect of cryptorchidism on fertility appears to begin before the onset of puberty, both hormonally and histologically. At 4 to 6 months of life, males undergo an androgen surge labeled “mini-puberty.” Hadziselimovic, Emmons, and Buser (2004) concluded that there is impaired transformation of germ cells into adult dark (AD)- spermatogonia – thought to be stem cells for later spermatogenesis – during mini-puberty in UDT. Zivkovic and Hadziselimovic (2009) suggest that UDTs do not undergo the usual mini-pubertal increase of Sertoli cells either, leading to diminished numbers overall.

Hypogonadotropic hypogonadism appears to be an underlying mechanism in the impaired “mini-puberty” response. Infants and children with cryptorchidism have lower basal LH and testosterone, with a blunted response to GnRH stimulation (Job et al., 1987). Fibrosis of the interstitium has since been identified (Hadziselimovic, 1977), as well as progressive deterioration of germ cells visible after the first six months of life. Patient age and whether the cryptorchid testis is palpable have been predictive of severity of histologic changes on biopsy (Tasian, Hittelman, Kim, DiSandro, & Baskin, 2009). An argument for orchiopexy, particularly early orchiopexy, is that UDTs remaining undescended were associated with progressive loss of germ and Leydig cells; nonpalpable testes predicted severe germ cell loss.

**Treatment.** The goal for treatment of UDT is a testis within the scrotum without atrophy. Hormonal therapy involves hCG, gonadotrophin-releasing hormone (GnRH), and their synthetic analogues, shown in randomized control trials to have variable efficacy. In a multicenter study, overall success in inducing testis descent was 21%, 19%, and 4% for GnRH, hCG, and placebo, respectively (Christiansen et al., 1992).

Orchiopexy is recommended in the United States by 1 year of age (Korkorowski, Routh, Graham, & Nelson, 2010) if the UDT does not spontaneously descend before 6 to 12 months of life, with hopes of preserving spermatogonia and minimizing damage to seminiferous tubules. The European Association of Urology recommends that orchiopexy be performed at the latest by 12 to 18 months of age (Tekgül et al., 2011). The success rates of orchiopexy range from 85% to 95% (Thorup et al., 2007). Techniques include inguinal, laparoscopic, microsurgical, and transcrotal approaches. Staged orchiopexy (Fowler-Stephens procedure) can be performed when the spermatic cord or vessels are not long enough to properly mobilize the testis into the scrotum. Despite surgical treatment, long-term outcomes of impaired fertility and increased cancer risk are still higher than in boys without UDT.

**Acquired Insults**

**Acquired insults impacting
male fertility include testicular torsion, incarcerated hernia inguinal hernia (interrupting testicular blood flow), and trauma or rupture of the testis or any component of the male reproductive system. Ischemia or reperfusion injury, development of immunologic infertility, and obstruction from scar tissue are major contributing mechanisms. Infectious causes include mumps orchitis in the post-pubertal male. In a study of adolescent youth (age 14.9 +/- 1.0 year) in the United States, Durant, Rickert, Ashworth, Newman, and Slavens (1993) found that 6.5% reported using steroids without a physician’s prescription. These children were likely to use other drugs, such as cocaine, smokeless tobacco, and marijuana. The reproductive effects of anabolic steroids may not be permanent and may reverse with discontinuation of the steroids (National Institute on Drug Abuse, 2006). Cocaine use has been associated with oligospermia and defects in sperm morphology and motility (Bracken et al., 1990; Hurd et al., 1992). Cigarette smoking may have adverse effects on male fertility by reducing sperm production, motility, and morphology. Smoking tobacco may also lead to the development of pyospermia, decreased sperm penetration, and hormonal alterations (Nudell, Monoski, & Lipshultz, 2002; Sigman, 2007; Thonneau et al., 1991; Vine, Margolin, Morrison, & Hulka, 1994).

Testicular Torsion

Torsion of the spermatic cord is a common urologic emergency among adolescent males and a risk factor for infertility. Interruption of testicular blood supply in complete torsion can cause irreversible ischemia requiring orchiectomy. If diagnosed and corrected surgically within six hours, the testis is usually salvageable. However, long-term damage may occur despite timely correction by various mechanisms. The blood-testis barrier is damaged, and the immune system becomes inoculated with testis antigens and anti-sperm antibodies that cause immunologic infertility during reproductive years.

Prepubertal torsion does not appear to impact fertility because the contralateral testes undergo normal development (Puri, Barton, & O’Donnell, 1985). Further, torsion in the prepubertal male does not cause autosensitization and diminished fertility in adult life.

Evaluation. Patients are often prepubertal or early postpubertal males who present to the emergency department with sudden onset severe lower abdominal or scrotal pain with scrotal swelling. Physical findings include an edematous, extremely tender testis, which may be elevated or retracted compared to the contralateral size due to shortening of the cord. The cremasteric reflex is usually absent on the torsed side.

Because the treatment for torsion is surgical, it is important to distinguish this from other etiologies of scrotal pain, such as orchitis, epididimitis, torsion of the appendix testis, and testicular trauma. Technetium-99m pertechnetate scans, and color Doppler ultrasound have been used to differentiate infectious or inflammatory causes from torsion based on blood flow patterns; the former shows increased flow, the latter ischemia. Ultrasound is easier to obtain and more cost-efficient than nuclear imaging (see Figure 2) (Karadeniz et al., 1996). When history, physical examination, and imaging are not adequate, surgical exploration provides a definitive diagnosis and is the appropriate treatment.

Management. The clinician may first attempt manual reduction of the torsed cord, but immediate surgical exploration is still required. If detorsed within six hours, up to 90% of patients may
have testicle salvage; at 24 hours, however, salvage rates drop to 10% (Tryfonas et al., 1994). Bilateral orchiopexy is indicated for acute torsion of the spermatic cord because bilateral involvement is common, especially in males with the “bell clapper” deformity who have failure of normal anchoring of the testis. In these and other patients, there is high risk of recurrent torsion, threatening fertility.

**Impact on fertility.** Post-pubertal unilateral testicular torsion appears to be responsible for inducing pathologic changes in both testes. While duration of torsion determines initial ischemia, surgical correction may contribute to ischemia/reperfusion injury and oxidative stress that further impairs spermatogenesis (Minutoli et al., 2009; Turner, Bang, & Lysiak, 2004). Various studies have highlighted more insidious mechanisms of testis damage: breakdown of the blood-testis barrier causing immunologic infertility (Merimsky, Orni-Wasserlauf, & Yust, 1984), extensive apoptosis in the contralateral testis via cytokine release (Hadziselimovic, Geneto, & Emmons, 1998), and most recently, late impairment of both endocrine and exocrine functions of the testis (Romeo et al., 2010).

**Malignancy and Infertility**

Malignancy in childhood and adolescence can have a significant effect on future male reproductive capacity. The cancer itself may diminish fertility, and treatment modalities may cause temporary or permanent azoospermia. It is extremely important to discuss fertility preservation with adolescents who are at risk and their parents. Studies have demonstrated that pediatric and adolescent oncology patients are often surprised to learn about cancer-related infertility, and future parenthood is a significant consideration in this population (Schover, Brey, Lichtin, Lipshultz, & Jeha, 2002a, b). Nurses and midlevel providers may be useful in educating oncology patients and their parents so they may move beyond their initial diagnosis and pursue sperm banking if interested.

Testicular germ cell cancer (TGCC) is the most common malignancy in Caucasian males, starting in late teenage years. TGCC may have an adverse effect on semen quality (Petersen, Skakkebaek, Vistisen, Rorth, & Giwercman, 1999) and contribute to the development of hypogonadism through Leydig cell dysfunction (Nord et al., 2003), even in the contralateral testis. Treatment often requires local or total body irradiation at doses that can cause infertility. Similarly, chemotherapy used in the treatment of TGCC may also have an effect on spermatogenesis. Not all testicular tumors in childhood and adolescence are malignant; efforts to preserve testicular tissue are being used more frequently for benign testicular lesions, such as epidermoid tumors, which are often identified preoperatively based on ultrasound appearance (see Figure 3).

Regardless of the location of the malignancy, pre-pubescent males receiving chemotherapy may be at risk for a cytotoxic insult to the rapidly dividing spermatogonia. This temporary impairment can last up to two years (Levine, Canada, & Stern, 2010). Permanent infertility may result due to the quantitative and qualitative damage to spermatogenic germ cells, particularly with the use of higher-dose alkylating agents.

**Sperm Cryopreservation**

Before chemotherapy for any malignancy, orchectomy or radiation therapy in the vicinity of the reproductive organs or total-body irradiation, sperm cryopreservation should be considered and discussed with the adolescent and family because it is the best-established and least-invasive means of preserving fertility in adolescent patients. If mastur-
bation with ejaculation is not a suitable option due to age, discomfort, or illness, other more invasive options exist. Microsurgical epididymal sperm aspiration, testicular sperm extraction, or electroejaculation under anesthesia can be performed for sperm retrieval for cryopreservation. These procedures may provoke anxiety for the child or adolescent as well as the parents, and thus, education and counseling are critical. Urology nurses can be invaluable in helping these individuals get through such anxiety-provoking and emotional experiences by helping the patient and family interpret complicated data and procedures to help make their best decision.

**Hormonal/Metabolic Disturbances**

Hormonal or metabolic causes of infertility in adults include growth hormone deficiency, hyperprolactinemia (such as pituitary adenoma), and thyroid abnormalities. Aside from growth hormone deficiency, these conditions are not typically identified in younger pediatric patients, such as those with Klinefelter syndrome.

**Conclusion**

While the adult male infertility workup may be a familiar evaluation, many factors affecting fertility can be traced back to early adolescence, childhood, the newborn period, and even the preimplanted embryonic state. Common diagnoses identified in childhood and adolescence may have an impact on fertility. An understanding of the presentation, evaluation, and management of these conditions is essential because their potential impact on fertility is critical to the overall care of these children/adolescents and their families.

Advances in the treatment of infertility present opportunities for cryopreservation and future fertility in many children. Since the discussion of infertility may provoke anxiety for both the affected child or adolescent and the parent(s), it is important that physicians and nurses caring for these individuals be aware of the emotional impact that may be associated with these conditions and be prepared to educate, counsel, and support the family to alleviate their anxieties and concerns.

**References**


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N RESPONSE TO IDEAS from SUNA members and the Urologic Nursing Editorial Board, as well as the recent commitment by schools of nursing across the country to the White House’s Joining Forces initiative (www.whitehouse.gov/joiningforces), Urologic Nursing will publish a special issue focused on the urologic health care needs of our nation’s veterans and active duty service members. Urologic nursing professionals may encounter combat-related mental health and physical challenges experienced by returning soldiers and their family members in clinical settings affiliated with the Department of Veterans Affairs (VA) and non-VA health care settings. We believe it is important to share our clinical experiences and expertise as one step in supporting our veterans – they have supported us by serving in the military.

Please contact Editorial Board Members Christine Bradway or Kaye K. Gaines with your manuscript ideas and thoughts about this very special issue!

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