Physical deformities relevant to male infertility

Rajender Singh, Alaa J. Hamada, Laura Bukavina and Ashok Agarwal

Abstract | Infertile men are frequently affected by physical abnormalities that might be detected on routine general and genital examinations. These structural abnormalities might damage or block the testes, epididymis, seminal ducts or other reproductive structures and can ultimately decrease fertility. Physical deformities are variable in their pathological impact on male reproductive function; some render men totally sterile, such as bilateral absence of the vasa deferentia, while others cause only mild alterations in semen parameters. Concise and up-to-date information regarding the contemporary epidemiological characteristics, clinical features and pathophysiological impacts of these common abnormalities on male fertility is crucial for the practicing urologist to identify the best treatment option.

Rajender, S. *et al*. *Nat. Rev. Urol.* **9**, 156–174 (2012); published online 21 February 2012; doi:10.1038/nrurol.2012.11

Introduction

Physical deformities of the male reproductive tract are structural abnormalities that can damage or block the testes, epididymis, seminal ducts, or prostatic utricles and ultimately decrease fertility. These deformities differ in their pathological impact on male reproductive function; some render men totally sterile (such as bilateral absence of the vasa deferentia) while others produce only mild alterations in semen parameters (such as hydrocele). Other physical abnormalities, such as inguinal hernia, may not result in male infertility directly, but are commonly associated with other fertility-threatening conditions. Moreover, surgical repair of inguinal hernia can also result in male infertility. For the practicing urologist, it is important to identify deformities so that adequate treatment can be instituted promptly.

In this Review we will describe a number of common deformities of the male reproductive tract that either commonly occur in infertile men or are potentially associated with male infertility. We will describe disorders of the testes, scrotum, epididymis, vasa deferentia, ejaculatory ducts and prostate, and will discuss how they negatively affect male fertility, providing a brief outline of the available treatment options. Penile abnormalities (including hypospadias, epispadia, phimosis, and penile deviation) are outside the scope of this article, and will not be discussed.

Testicular disorders

Cryptorchidism

Cryptorchidism is the absence of one or both testicles from their normal scrotal position, which is predominantly due to failure to descend through the normal anatomical pathway. Although cryptorchidism is one of the most common congenital abnormalities of the male reproductive system,[1] its prevalence is a matter of controversy. Recent reports indicate an increase in prevalence over the last 10–15 years, particularly in industrialized countries. Older studies reported that cryptorchidism affected nearly 3% of all full-term male infants[2] and 7.5–30% of premature infants, who are at higher risk because the testes descend in the last trimester of pregnancy.[3,4] Because testicular descent can also occur within the first 3 months of life—attributed to a brief period of endogenous testosterone secretion—the prevalence of cryptorchidism in 1-year-old infants tends to be lower, previously reported at 0.8–1.0%.[5] However, a recent epidemiological study in the UK has demonstrated that in the period between 2001 and 2008 the prevalence of cryptorchidism at birth was 5.3% for full-term infants, and 14% for preterm infants.[6] Despite a reduction in the high initial prevalence of the condition among full-term infants to 2.4% at 3 months, a surprising subsequent rise to 6.7% was recorded at 12 months. This rise is explained by the emergence of new cases of acquired cryptorchidism, also known as testicular ascent (see later). Similarly, the prevalence of cryptorchidism at birth in Denmark between 1997 and 2001 has increased from 1.8–2.0% to 9%.[7] However, a small prospective cohort study from a single institution in Denmark examined the prevalence of cryptorchidism among 1,094 boys from birth to the age of 4 years, and failed to show any difference in the prevalence of cryptorchidism from previous reports.[8] Surprisingly, the condition has been observed in 0.5–0.6% of adult men, as reported from several countries, including Hungary and Jordan.[9,10]

The cause of such a rise in incidence of cryptorchidism is partly attributed to increased detection of acquired cryptorchidism and partly to the increased prevalence of congenital cases. Environmental factors such as maternal exposure to smoking and endocrine disruptors (plasticizers, fertilizers, industrial exhausts) have been implicated in the rise of congenital cryptorchidism. The etiology of cryptorchidism is thought to be multifactorial and it is

Central Drug Research Institute, Lucknow 226001, India (**R. Singh**). Center for Reproductive Medicine, Glickman Urological and Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA (**A. J. Hamada**, **L. Bukavina**, **A. Agarwal**).

Correspondence to:
A. Agarwal
agarwaa@ccf.org

Competing interests
The authors declare no competing interests.

usually not possible to verify a specific cause. Virtanen *et al.*[11] have hypothesized that cryptorchidism is a variable manifestation of testicular dysgenesis syndrome.[11] This theory is based on epidemiological studies that revealed a high incidence of testicular cancer in countries with high frequencies of cryptorchidism, hypospadias and poor semen quality. Although epidemiological evidence exists to support this theory, full molecular analysis and genetic linkage have not been critically analyzed and the issue remains unresolved.

Cryptorchidism can be categorized as isolated or syndromic (Box 1). Isolated cryptorchidism is observed in approximately 85% of affected patients and can be further divided into congenital or acquired subtypes. Congenital type is usually diagnosed at birth based on the failure of testicular descent. Acquired cryptorchidism is a relatively new concept, denoting the upward ascent of testicles from their normal scrotal location, and should be carefully differentiated from secondary ascent of the cryptorchid testis after orchiopexy, which is known as recurrent cryptorchidism. The underlying mechanism of acquired cryptorchidism is not entirely understood. Hypotheses include failure of the spermatic cord to elongate concurrently with growth in body height, and partial involution of a patent processus vaginalis resulting in the formation of a fibrous cord. The exact prevalence of acquired cryptorchidism in young boys is still under investigation, and current data indicate that its prevalence is variable among different developmental ages. Acerini *et al.*[6] reported prevalences of 0.7%, 4.0%, 1.3% and 1.0% at 3, 12, 18 and 24 months, respectively,[6] whereas Sijstermans *et al.*[12] demonstrated prevalences at 6 years, 9 years and 13 years of 1.2%, 2.2% and 1.1%, respectively.[12] These data do not support an age-related increase in incidence of acquired cryptorchidism; however, by taking into account the variation in height of individuals at these ages, an association between increased rate of growth in height and acquired cryptorchidism might be assumed. Spontaneous testicular descent is likely to occur in patients with acquired cryptorchidism during early puberty owing to the related testosterone surge.

In syndromic cryptorchidism, undescended testes are a sign of a specific condition, such as disorders of the hypothalamic–pituitary–gonadal axis or syndromes of testosterone secretion and action. Syndromic cryptorchidism can also occur in association with lax abdominal wall musculature and reduced abdominal tension, in conditions such as prune belly syndrome, gastroschisis and bladder exstrophy.

While it is well known that cryptorchidism—whether syndromic or isolated, congenital or acquired—can result in low sperm concentration, low sperm count and infertility, the extent of damage varies according to a number of factors, including testis location, temperature, hormone levels and associated structural anomalies (Box 2).

Location of the testes is crucial to fertility status; the higher the testes, the higher the risk of infertility. Therefore, patients with abdominal testes are at the greatest risk of infertility.[13,14] In a study of children with unilateral cryptorchidism, it was demonstrated that the undescended testis had a higher temperature than the contralateral testis.[15] Accordingly, studies on experimental cryptorchidism in monkeys have demonstrated that elevated undescended testicular temperature results in immaturity and functional alteration of Sertoli cells—the essential nurturing and supporting cells for sperm. High temperatures can also impair the integrity of the blood–testis barrier and induce germ cell apoptosis.[16,17] Oxidative stress has been postulated as an important mediator of thermal damage to testicular tissue.

Infertility has also been attributed to insufficient development of type A dark spermatogonia (sperm progenitor cells) from the gonocytes.[18] The production of these spermatogonia is testosterone dependent[19] and it is hypothesized that lack of the brief testosterone rise after birth (postnatal minipuberty) might underlie this defective transformation in boys with cryptorchidism. Furthermore, Wolffian duct anomalies and urogenital nonunion abnormalities have been reported in association with cryptorchidism. Vasal and epididymal agenesis, segmental atresia, long looping epididymis and nonfusion or incomplete fusion between the epididymal caput and rete testis have been noted in 35–68% of boys with cryptorchidism.[20,21] Such anomalies are more commonly observed in children with bilateral and nonpalpable cryptorchid testes, and might jeopardize the transport of already insufficiently produced sperm (Box 2).

Key points

- Physical deformities of the male reproductive tract are physically evident structural abnormalities that can damage or block the testes, epididymis, seminal ducts and other reproductive structures
- Paternity rates in men with a unilateral undescended testicle are similar to those of healthy men, whereas those who have undergone bilateral orchiopexy for cryptorchidism have a paternity rate of 46–65%
- Clinical presentations of infertile men with previous testicular torsion include unilateral or bilateral anorchia, unilateral testicular atrophy, oligozoospermia, oligoasthenoteratospermia and nonobstructive azoospermia
- Unilateral or bilateral clinical varicocele is associated with defective endocrine and exocrine testicular and epididymal functions as well as sperm dysfunction
- Incidence of hydrocele in infertile men is 3.2%, constituting the third most common ultrasonographically-detected scrotal abnormality after varicocele and epididymal cyst
- Infertility among men with autosomal polycystic kidney disease is common and has multiple pathologies

Box 1 | Types of cryptorchidism

Isolated cryptorchidism (85%)
- Congenital
- Acquired

Syndromic cryptorchidism (15%)
- Caused by hypothalamic and pituitary abnormalities, such as Kallmann syndrome, isolated hypogonadotropic hypogonadism and Prader–Willi syndrome
- Disorders of testicular testosterone secretion, such as Klinefelter's syndrome, testicular dysgenesis syndrome, Noonan syndrome and congenital adrenal hyperplasia
- Disorders of testosterone action, such as androgen insensitivity syndrome
- Congenital disorders that result in poor development of abdominal musculature and lack of muscle tension, such as gastroschisis, omphalocele, bladder exstrophy and prune belly syndrome

Box 2 | Mechanisms of infertility in cryptorchidism

Effects on germ cells
- Heat-induced oxidative stress*
- Pachytene spermatocytes and spermatids undergo apoptosis
- Spermatogonia show signs of cell cycle arrest and thermotolerance*
- Reduction in the number of type A dark spermatogonia and spermatogonia B, the essential progenitor of sperm in the abdominal testes

Effects on Sertoli cells
- Morphological and functional alterations
- Reversion to immature and dedifferentiated stage in the cryptorchid testis, and thus loss of its supportive role in spermatogenesis
- After heat stress, increased expression of cytokeratin 18, liver receptor homolog-1 and intermediate filaments*
- After heat stress, decreased expression of androgen receptor and junction-associated proteins such as zonula occludens-1 and occludin*
- No apoptosis is seen in Sertoli cells
- The above changes result in disruption and an increase in the permeability of the blood–testis barrier and henceforth loss of its protective role

Effects on Leydig cells
- Relatively resistant to the effect of heat
- Other mechanisms underlie the finding of low testosterone level in men with bilateral cryptorchidism

Effects on Wolffian duct
- Vasal and epididymal agenesis
- Nonunion or incomplete fusion between epididymal tubules in the caput and the rete testis
- Segmental atresia in the vasa deferentia and the epididymis
- Long looping of the epididymis and increased vulnerability to injury during orchiopexy

*In experimental animal models.

Other important factors that influence infertility are whether cryptorchidism is unilateral or bilateral and whether orchiopexy is performed before 3 years of age. In one study, half of men presenting with unilateral cryptorchidism had a normal sperm concentration compared to only 25% of those with bilateral cryptorchidism.[22] Analysis of semen from men with untreated bilateral cryptorchidism revealed that affected men were more likely to have azoospermia and higher levels of testicular germ cell apoptosis than men with untreated unilateral cryptorchidism.[23,24] Moreover, 44–100% of men with treated bilateral cryptorchidism have been reported to have a low sperm count (<20 million cells/ml), as well as sperm with poor motility and abnormal morphology, and more than 50% are azoospermic.[1]

Generally, three important parameters are assessed to examine fertility potential in men with a history of cryptorchidism: semen quality, paternity rate and time to conception (Table 1). However, the predictive power of semen analysis is not absolute and men with mild-to-moderate oligozoospermia are often able to achieve pregnancy. On the other hand, men with normal semen parameters have only a 60% chance of paternity.[25] Thus, paternity rates and time to conception are more demonstrative of reproductive problems among men with cryptorchidism than semen quality. Although men with a unilateral undescended testicle (treated or untreated) often have abnormal semen parameters, their paternity rate is similar to men with bilateral normal testes.[26] On the other hand, in men with bilateral cryptorchidism who underwent bilateral orchiopexy before they were 3 years of age, the paternity rate varies between 46% and 65%, with a longer time to conception than controls (33.9 months versus 8.8 months; $P = 0.0003$).[27,28] Lee *et al.*[29] calculated relative infertility risk in men with treated bilateral cryptorchidism and found that these men are six times more likely to be infertile than men in the general population.[29] Although early orchiopexy improves the paternity rates and semen analyses of men with previous bilateral cryptorchidism, its role in unilateral cryptorchidism is less important.

In terms of treatment, the current consensus—based on better fertility rates and lower incidence of testicular cancer—is to perform early orchiopexy at 6 months old for children with unilateral or bilateral undescended testes.[30] For palpable undescended testes in the inguinal region, open inguinal exploration and orchiopexy is advised. For abdominal testes, laparoscopic exploration with orchiopexy or orchiectomy is performed based on the severity of testicular damage. Hormonal therapy is generally less successful than the other forms of therapy.[30]

As mentioned previously, men with a unilateral undescended testis are usually fertile, although a significant portion of them may have oligozoospermia. Infertility in these men should raise the suspicion of associated bilateral epididymal nonfusion abnormalities, presence of syndromic cryptorchidism and its underlying endocrinopathy, or other complicating factors that affect sperm production in the normally descended testis, such as varicocele, adverse environmental factors, trauma, infection and hormonal defects. If identification and correction of an evident etiology does not result in a marked improvement in semen parameters, the next step is to use assisted reproductive techniques. In the presence of severe oligozoospermia (sperm count less than 5 million cells/ml), the physician may advise sperm cryopreservation and *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) using fresh or frozen sperm. Similarly for men with nonobstructive azoospermia and previous unilateral orchiopexy, identification of the etiologies mentioned above and treatment may help in the return of sperm to the ejaculate. Otherwise, sperm retrieval from the normal testis and IVF or ICSI is recommended.

For men with a history of bilateral orchiopexy, unassisted paternity is reported in up to 65% of patients.[31] Semen retrieval and IVF or ICSI are used to achieve pregnancy for men with moderate or severe oligozoospermia. Successful testicular sperm extraction from azoospermic men with history of bilateral orchiopexy is reported in up to 60% of cases, which is comparable to sperm retrieval rates in men with nonobstructive azoospermia due to other reasons.[32] An azoospermic adult man presenting with unilateral or bilateral undescended testes should undergo orchiopexy, which is reported to result in return of sperm to the ejaculate and spontaneous pregnancy.[33] When orchiopexy is considered in adults and children, frequent examination of the replaced testis is of paramount importance to detect any abnormal nodularity, irregularity or mass that might raise suspicion of testicular cancer.

Table 1 | Semen analyses, paternity rates and time to conception among men with cryptorchidism

Cryptorchidism	Oligozoospermia (%)	Azoospermia (%)	Normal semen analysis (%)	Paternity rate (%)	Time to conception (months)
Unilateral					
Untreated	47[259]	7–17[22,260]	55–95[261,262]	80–90[263,264]	11.1[265]
Treated	21–64[259,260]	7–17[22,260]	55–95[261,262]	80–90[263,264]	11.1[265]
Bilateral					
Untreated	5–10[23]	89[23]	NR	NR	NR
Treated	31–65[22,262]	32[266]	25–30[260,262,267]	48–65[31]	33.9[265]

Abbreviation: NR, not reported.

Microorchidism

Development of the testes is characterized by dramatic dynamic growth changes between birth and puberty. Newborn boys normally have testes that measure about 1 ml in volume. During the first 2 months of life, the testes enlarge owing to the brief postnatal testosterone surge, and then shrink slightly, remaining about 1–2 ml until the onset of puberty.[34] Testis enlargement is the first sign of puberty in boys, and progressive growth characterizes the subsequent pubertal stages.[35] The most striking change is the increase in seminiferous tubule diameter (from 50 μm to 200 μm) owing to enhanced germ cell proliferation. The normal average volume of a single adult testis is 18 ml[36] with a normal range of 12–30 ml.[37]

Microorchidism is a congenital or acquired condition in which testicular volume is less than two standard deviations below the mean for healthy boys at a specific age and developmental stage.[38] Low testicular volume can be due to either the testes failing to grow (testicular hypoplasia) or regressive changes after normal size has been reached (testicular atrophy). Microorchidism can be unilateral or bilateral, and can affect prepubertal and postpubertal male patients. Unilateral hypoplastic testis is uncommon at birth and is usually the result of a partial or complete antenatal ischemic event.[39] Bilateral hypoplastic rudimentary testes are often associated with congenital syndromes such as Klinefelter syndrome and Prader–Willi syndrome, and with abnormalities of the hypothalamic–pituitary–gonadal axis.[40,41] Testicles also fail to grow in patients with cryptorchidism and in adolescents with large varicoceles. 19.0%, 28.6% and 38.0% of boys with cryptorchidism have smaller than normal testes at puberty stages P3, P4 and P5, respectively,[42] and 33–55% of boys with large varicoceles have small ipsilateral testes.[43–45] Rare cases of mixed gonadal dysgenesis can present with a male phenotype and unilateral hypoplastic testis. Testicular atrophy, on the other hand, affects the scrotal testis secondary to a wide array of causes such as testicular torsion, previous hernia repair with partial vascular compromise, administration of anabolic steroids, and radiation.[46]

Diagnosis of microorchidism is readily achieved clinically via palpation and orchidometer and is confirmed by scrotal ultrasonography. Decreased testicular size, whether unilateral or bilateral, is correlated with impaired spermatogenesis, and bilateral microorchidism (the most commonly observed) results in sterility.[46]

Testicular size relates closely to sperm count and morphology because the seminiferous tubules and germinal elements make up nearly 80% of testicular volume.[47] Adult testes consist of two major compartments: the interstitial compartment, which constitutes 15–20% of testicular volume, and the tubular compartment (composed of germ cells and Sertoli cells) that forms about 60–80% of testicular volume. Although Sertoli cells account for only 35–40% of seminiferous tubule epithelium, they are the major determinant of testis size. The final number of mature Sertoli cells in the adult testis is established by fetal, neonatal and peripubertal proliferation with a relatively low rate of apoptosis.[48] Each cell supports a species-specific number of proliferating germ cells—10 germ cells in humans.[49] As such, adult testis size, spermatogenesis and sperm output are ultimately based upon the number of mature Sertoli cells. Abnormal testicular size can be noted in both prepubertal and pubertal male patients, although identification of such abnormalities at birth may not be an accurate prediction of testicular size in adulthood. Management of patients with microorchidism is based on treating the underlying pathology.

Polyorchidism

Polyorchidism is an extremely rare congenital anomaly marked by the presence of one or more extra testes, thought to result from either duplication of the mesodermal ridge or premature division of the ridge into two or more elements, each of which has the potential to form a testis.[50] The observation that both normal and ipsilateral extra testes have a common proximal blood supply[51] and the finding of a bilobed testis as a result of incomplete separation of the genital ridge, support this theory. The supernumerary testis usually has a separate vas deferens and epididymis, although a common vas deferens has been reported. Over 100 case studies have been recorded in the literature.[52]

Singer *et al.*[53] originally classified polyorchidism into two types based upon anatomical and functional properties of the extra testis.[53] In type 1 polyorchidism—accounting for 90% of cases—the supernumerary testis is attached to the draining seminal ducts (epididymis and vas deferens) and has reproductive potential. The extra testis in type 2 polyorchidism has no such attachment and has no reproductive potential. Each of these types can be further subdivided into Group A and Group B

according to whether the extra testis is in the scrotum (referred to as orthotopic or intrascrotal) or outside the scrotal sac (known as ectopic or cryptorchid), respectively.[53] Since then, a new classification model has been proposed by Bergholz *et al.*[54] based on the presence and characteristics of the functional outflow tract.[54] According to this model, type A indicates that the supernumerary testicle has an outflow seminal duct (vas deferens), and is further divided into A1 (testis has its own vas deferens and epididymis), A2 (testis possesses its own epididymis but shares a common vas deferens with ipsilateral adjacent testis), A3 (shares a common epididymis and vas deferens with neighboring testis) and A4 (shares a common epididymis with other testis but has a separate vas deferens). Extra testes that lack a vas deferens are denoted Type B, and can be further subdivided depending on whether the testes has an epididymis (B1) or not (B2).[54]

Clinically, triorchidism is the most common presentation. Most cases are discovered incidentally during evaluation of men with undescended testes, inguinal hernia or infertility. Approximately 75% of affected patients have a painless intrascrotal mass. Testes are inguinal in 20% of patients, and retroperitoneal in 5%.[55] Men aged 15–25 years are mostly commonly affected,[56] and left-sided polyorchidism is three times more predominant than right-sided polyorchidism.[56]

Although polyorchidism is a reported cause of vasectomy failure and testicular tumor,[57] infertility is also a common finding in affected men. Histological evaluation reveals that 37% of men with polyorchidism have tubular atrophy, a Sertoli cell pattern (without Leydig cells) or a lack of spermatogenesis.[58] The etiology of polyorchidism-related infertility is unknown; however, abnormal spermatogenesis, in both the extra testis and normal testis, may be attributed to embryonic genital ridge insult resulting in abnormal testicular development or recurrent postnatal vascular compromise of the normal testis. Both homolateral testes (the extra and the normal testes) might experience recurrent vessel kinking and torsion episodes, owing to high incidence of bell clapper deformity (high insertion of tunica vaginalis on spermatic cord), abnormal testicular vasculature and aberrant seminal duct connections to the ipsilateral testis.[59]

Abnormal testicular germ cell development and proliferation have been studied by Francesco *et al.*,[60] who performed histochemical analysis on the testes from a patient with A1 triorchidism (according to the Bergholz model). The investigators found that the lower normal testis had lower expression of Sertoli cell marker CD99, fewer spermatogonia, and fewer germ cells than the upper extra testis.[60] Moreover, significant levels of hypospermatogenesis and germ cell apoptosis have been demonstrated in the lower testis, compared with upper ipsilateral testis, as evidenced by reduced c-kit immunolabeling in seminiferous tubules—a receptor protein that mediates the proliferative and antiapoptotic effects of stem cell factor.

The optimal management of patients with polyorchidism remains controversial, especially when the condition is discovered incidentally. Orchiectomy of the extra testes in adults helps confirm the diagnosis and reduces the risk of tumor formation.[61,62] The use of conservative treatment versus surgery depends on age, reproductive potential, suspicion of neoplasia, position of the testis (scrotal or ectopic), and the presence of torsion.[63] There is no need for surgical intervention in asymptomatic fertile polyorchid men. Instead they can be managed with close observation and physical examination, tumor marker assessment to exclude malignancy, and imaging studies (ultrasonography or MRI). Surgery is sometimes contemplated in cases of cryptorchidism with complications. Orchiopexy with testicular biopsy should be performed in men with associated cryptorchidism. Orchiopexy for both homolateral testes is suggested to reduce the risk of vascular insults. If pathologic evaluation shows no spermatogenesis, the patient has symptoms suggestive of testicular torsion or there is suspicion of malignancy, orchiectomy should be performed.[64]

Disorders of testicular circulation

Testicular torsion

Testicular torsion is an acute urological and andrological emergency, in which twisting of the spermatic cord results in progressive impairment of testicular venous drainage ultimately culminating in arterial ischemia and testicular infarction. The condition affects 1 in 4,000 men in total, and 1 in 158 men under the age of 25 years; it is most common in boys aged 12–16 years.[65,66]

Four types of testicular torsion exist, depending on which part of the anatomy is twisted. Extravaginal torsion is twisting of the spermatic cord and testis with its covering of the tunica vaginalis. It is the most common type of torsion to occur in the prenatal and neonatal period, but can also occur in older patients.[67] The connection between the spermatic cord and the cremasteric muscles does not develop until 30 days after birth, allowing the testis a large degree of movement. Because of this, almost 70% of pediatric extravaginal torsions occur during this time period.[68] Intravaginal torsion, on the other hand, is caused by a twisting of the testicle within the tunica vaginalis. This rarely occurs in a testis with normal anatomy, because the posterior aspect of the testis is attached to the scrotum. However, congenital anomalous high insertion of the tunica vaginalis into the spermatic cord results in a freely mobile testis and bell clapper deformity.[68] This anomaly is frequently bilateral. Other causes of intravaginal torsion include hypermobile testes, increased testicular volume (during adolescence), and cold temperatures. Torsion can occur at any age, but is most common between the ages of 12 and 18 years.[69] The third type of testicular torsion involves twisting of an abnormally long vascular mesorchium—the vascular ligament that attaches the posterior surface of the testis to the epididymis and posterior scrotal sac. This anomaly is common in cryptorchid testes, and allows the testis to rotate freely.[70] The final type, appendicular torsion, involves torsion of small remnants of the Müllerian duct that often persist on the superior pole of the testis

Table 2 | The fertility potential of patients treated for testicular torsion

Study	Type of therapy	*n*	Post-treatment		
			Semen analysis	Hormone profile	Other findings
Anderson *et al.*[74]	Detorsion	9	Normal	Increased FSH	NR
Anderson *et al.*[74]	Orchiectomy	7	Abnormal	Increased FSH	NR
Ichikawa *et al.*[75]	Detorsion	12	Normal	Increased FSH	NR
Ichikawa *et al.*[75]	Orchiectomy	12	Abnormal	Normal FSH	NR
Arap *et al.*[96]	Detorsion	9	Abnormal	Normal FSH, LH and testosterone	Negative for antisperm antibody
Arap *et al.*[96]	Orchiectomy	15	Abnormal	Normal FSH, LH and testosterone	Negative for antisperm antibody
Taskinen *et al.*[82]	Detorsion	11	NR	19% abnormal FSH or inhibin	NR
Taskinen *et al.*[82]	Orchiectomy	6	NR	67% abnormal FSH or inhibin	NR
Shafik *et al.*[268]	Detorsion	8	Abnormal ($n=7$)	NR	NR
Tryfonas *et al.*[76]	Detorsion*	18	Abnormal	NR	61% developed testicular atrophy
Tryfonas *et al.*[76]	Orchiectomy*	7	Abnormal	NR	NR
Rybkiewicz[85]	Detorsion	8	NR	Abnormal FSH and LH Low testosterone	More than 50% of group developed antisperm antibody
Rybkiewicz[85]	Orchiectomy	29	NR	Abnormal FSH and LH Low testosterone	More than 50% of group developed antisperm antibody
Romeo *et al.*[83]	Detorsion	12	Abnormal ($n=4$)	Inhibin B markedly reduced	50% of group developed testicular atrophy
Romeo *et al.*[83]	Orchiectomy	8	Abnormal ($n=3$)	Inhibin B markedly reduced	NR
Fisch *et al.*[77]	Detorsion	11	NR	Abnormal response of FSH and LH to GnRH stimulation	60% developed testicular atrophy
Fisch *et al.*[77]	Orchiectomy	3	NR	Abnormal response of FSH and LH to GnRH stimulation	NR
Fu *et al.*[98]	Orchiectomy	10	NR	Inhibin B was reduced initially but restored after 3 months	Antisperm antibody elevated after operation
Brasso *et al.*[78]	Detorsion	31	Insignificant abnormalities	Raised FSH and LH in those with torsion duration >8 h	Testicular atrophy in 8% of those with <8 h of symptoms, 33% of those with 8–24 h of symptoms and 60% of those with >24 h of symptoms
Brasso *et al.*[78]	Orchiectomy	4	Insignificant abnormalities	Raised FSH and LH in those with torsion duration >8 h	Testicular atrophy in 8% of those with <8 h of symptoms, 33% of those with 8–24 h of symptoms and 60% of those with >24 h of symptoms
Daehlin *et al.*[84]	Detorsion	29	Normal	Normal FSH	NR
Daehlin *et al.*[84]	Orchiectomy	23	Normal	Elevated FSH	NR
Hagen *et al.*[89]	NR	55	87% abnormal	NR	88% developed testicular dysplasia in the contralateral testis

*Only 2 patients underwent semen analysis. Abbreviations: FHS, follicle-stimulating hormone; GnRH, Gonadotropin-releasing hormone; LH, luteinizing hormone; NR, not reported.

or epididymis. Clinical presentation of appendicular torsion is usually much less severe than intravaginal torsion in terms of pain, which is localized over the superior portion of the testis, nausea and vomiting, and can often be misinterpreted as epididymitis or epididymo-orchitis. To our knowledge, almost all studies performed to assess the fertility status of men with testicular torsion have been conducted on those with peripubertal torsion, which is most commonly intravaginal (Table 2).

Torsion is one of the leading causes of acute scrotal pain and male factor infertility. However, it is more likely that infertile men will present with the long-term complications of a torsion that occurred when they were younger, than present with acute testicular torsion itself. Such long-term complications include unilateral or bilateral acquired anorchia, unilateral testicular atrophy, oligozoospermia, oligoasthenoteratospermia and non-obstructive azoospermia. Despite low prevalence of a history of testicular torsion in infertile men (0.1–1.2%),[71] around 40–70% of men with a history of torsion have abnormal semen. Initial torsion obstructs venous return and persistent torsion compromises arterial pressure. The degree of ischemic trauma depends on the duration and degree of the torsion—rotation of the testes can range from 180° to >720°.[72] Ischemic injury is associated with free radical release, but it is currently unclear whether there is a relationship between duration of ischemia and semen quality.[73–78]

Ischemia and reperfusion injury causes germ cell apoptosis, testicular atrophy, and loss of spermatogenesis;[79] 6 h after the onset of impaired blood flow, the torted testis permanently loses spermatogenic capabilities, and 12 h after disrupted blood supply, the testis loses Leydig cell function.[68] In an experimental animal study, Leydig cell function (measured by testicular plasma testosterone concentration), was found to be significantly

lower after torsion.[80] However, this finding has not been reproduced in human studies except for in missed cases of bilateral torsion. The parameters used to assess fertility potential in men with prior testicular torsion include follow-up semen analysis, hormone profiles, testicular volume, testicular biopsy results and antisperm antibody measurements (Table 2). However, to our knowledge there are no controlled trials assessing paternity rate. The measured fertility markers show broad variation depending on the ischemic time (salvage rates), bilateral or unilateral involvement and type of treatment.

A double orchiectomy to remove necrotic torted testes certainly renders a man sterile, and unilateral testicular torsion has a negative impact on fertility, whether treated with orchiectomy or orchiopexy or left untreated. Although men with a solitary testis have normal paternity rates, the occurrence of oligozoospermia is higher than in men with two normal testes, and may reach up to 50% in men with testicular torsion. Oligozoospermia occurs in 70% of men who have undergone unilateral orchiectomy for previous testicular torsion.[81] Similarly, patients who have undergone detorsion (particularly those with ischemic time >8 h) demonstrate impaired semen quality on follow-up studies,[73] although research exists to suggest the reverse.[74,75]

Follow-up studies of men who have undergone orchiectomy[82–85] or detorsion[74,82,83] have demonstrated elevated follicle-stimulating hormone and low inhibin B (reflecting Sertoli cell mass) levels, but no evidence of low serum testosterone. Testicular biopsies taken from the contralateral testis at the time of torsion repair or several months later reveal germ cell apoptosis, desquamation of the germinal epithelium, and abnormal spermatogenesis in 57–100% of patients.[86,87] These observations support the theory that unilateral testicular torsion can cause bilateral testicular damage, but the inflicting mechanism is unclear because vascular supply to the testis is independent, and unilateral torsion does not affect oxygen concentration in the contralateral testis.[88]

Several theories have been suggested to explain the mechanisms of infertility in patients with testicular torsion, and the factors responsible for the fact infertility persists a long time after the acute episode. These include recurrent attacks of subclinical torsion affecting the contralateral testis, and the presence of foci of germinal epithelium that seem dysplastic and immature (with thin seminiferous tubular epithelium and atrophy of gonocytes, Sertoli cells and Leydig cells) in both testes, which may be responsible for abnormal spermatogenesis.[89]

The potential role of reflex vasoconstriction and ischemia followed by reperfusion injury in the contralateral testis has been demonstrated in various animal models.[90] Torsion involves both an ischemic and reperfusion component, both of which contribute to the production of reactive oxygen species (ROS). During reperfusion injury three sources of ROS production are activated: endothelial nitric oxide synthase is activated to produce nitric oxide;[91,92] cytokines (including tumor necrosis factor and interleukins 1 and 6) are released from blood and testis interstitial macrophages, causing chemotaxis, adhesion, diapedesis and interstitial infiltration of neutrophils;[93] and activated xanthine oxidase, converts accumulated hypoxanthine (derived from ATP) into uric acid in ischemic tissues and releases free radicals.[94,95] Uric acid and ROS are powerful pro-oxidants that play a part in microvascular injury, apoptosis, and tissue damage after ischemia.[96] Free radicals oxidize membrane lipids, induce cell death and DNA damage, and can ultimately lead to infertility.

Another hypothesis is that disruption of the blood–testis barrier in the torted testis results in immune sensitization against sperm. Human and animal studies provide evidence for the contribution of both humoral and cell-mediated immune sensitization against sperm. Antisperm antibodies, tumor necrosis factor, and interleukins 1 and 6 released from testicular macrophages, mast cells, lymphocytes and testicular somatic cells can lead to direct damage in the contralateral testis.[97,98] Nevertheless, <11% of post-torsion men have antisperm antibodies in their serum and semen,[74,89] so verification of the role of cellular immunity in clinical male infertility is still required.

Detorsion within 4–6 h of pain onset has been proven to salvage a torted testis in more than 90% of cases.[99] Testicular torsion usually occurs in the medial direction,[100] so manual detorsion under local anesthesia is attempted with manipulation away from the midline in the first instance. Loss of pain is considered an important sign of a successful maneuver.[69] After detorsion is confirmed by ultrasonography, the patient undergoes surgical exploration and bilateral orchiopexy to lower the testis and fix it in the scrotum.[69]

Given the potential role of cytokines and ROS in torsion-related infertility, pharmacological approaches to counter these factors have been attempted in experimental animal models with variable success (Box 3). Chemical sympathectomy has been used to abolish reflex contralateral vasoconstriction, and applying gradual detorsion to the spermatic cord has been suggested to prevent excessive generation of ROS and to allow host antioxidant defense to neutralize any oxidative rise. Similarly, applying ice packs can slow metabolism of the torted testis and prevent excessive release of free radicals. Other options include the use of immunosuppressive medications to prevent immune sensitization against sperm and to reduce the release of cytokines from inflammatory and testicular cells, and the use of antineutrophil agents to antagonize the neutrophils that mediate testicular injury. An essential strategy is to halt production of free radicals, which has been achieved with a variety of antioxidants and scavenging agents. Post-torsion therapy has been suggested to reverse or improve testicular histopathological changes in men with previous testicular torsion using hormonal therapy, such as human chorionic gonadotropin and dehydroepiandrosterone, or inhibitors of poly ADP-ribose polymerase, such as nicotinamide or trimetazidine, which deplete the cell of ATP in order to repair DNA damage. However, it must be noted that none of these treatment modalities have been tested in clinical studies on humans and their advantages are still theoretical.

In summary, conventional therapies for testicular torsion, such as detorsion or orchiectomy, may not be enough to rescue future fertility potential. As such, cytoprotective agents should be further investigated in human clinical trials to test their benefits for future reproduction.

Box 3 | Novel experimental modalities to treat torsion-related infertility

Chemical sympathectomy
Capsaicin, 6-hydroxy dopamine hydrobromide, guanethidine monosulfate.

Gradual detorsion
To prevent excessive generation of ROS and to allow host antioxidant defense to neutralize any oxidative rise.

Surface hypothermia
To slow metabolism of the torted testis and prevent excessive release of free radicals.

Immunosuppressive medications
Cyclosporine dexamethasone, hydrocortisone, prednisolone azathioprine, ibuprofen.

Antineutrophil agents
Dexamethasone, anti-E-selectin antibody, sivelestat, morphine.

Interfere with nitric oxide synthase
L-monomethylarginine.

Vasodilators
Papaverine, $MgCl_2$.

Counteracting oxidative stress
Korean red ginseng, coenzyme Q10, quercetin, montelukast, verapamil, lidocaine, lipid lowering agent (simvastatin and rosuvastatin), catalase, Cu-Zn SOD, catalase plus SOD and M40403 (a nonpeptide mimic of SOD), mexiletine, allopurinol, melatonin, propofol, raxofelast (vitamin E-like), vitamin C, lycopene, *Ginkgo biloba*, L-carnitine, L-carnitine and meloxicam (COX-2 inhibitor), N-acetylcysteine, curcumin, *Nigella sativa*, zinc aspartate, taurine, pentoxifylline.

Amelioration of germ cell apoptosis
Poly (ADP-ribose) polymerase (PARP) inhibitors (nicotinamide), sulfasalazine capsinoids, dehydoepiandrosterone trimetazidine, human chorionic gonadotropin.

Miscellaneous
Verdanafil and sildenafil, triazolopyrimidine (antianginal), darbepoetin-α (a novel erythropoietin protein), platelet-activating factor (PAF) antagonist, VIP, ethyl pyruvate, angiotensin-converting enzyme inhibitor (lisinopril), angiotensin II type 1 receptor blocker (losartan), hyperbaric oxygen therapy, surfactant tetronic 1107and peroxisome proliferator-activated receptor γ (PPAR-γ).

Varicocele

Varicocele is defined as abnormal dilatation and elongation of the internal spermatic veins and pampiniform plexus of the spermatic cord. Varicocele affects about 15% of the male US population.[101] Despite the fact that most adult varicoceles (>80%) have no effect on male infertility,[102,103] several studies suggest that a man with varicocele is at risk of subsequent loss of testicular function and fertility, regardless of normal semen analysis or documentation of previous fertility.[104,105] At the same time, varicocele is the most common correctable cause of male infertility, present in 40% of men with primary infertility and in up to 70% of men with secondary infertility.[106,107] The WHO have reported that 1 in 4 men with abnormal semen parameters has a varicocele, compared with 1 in 10 men with normal semen parameters.[108] Significant improvement in semen parameters after varicocele repair has been achieved in more than 50% of affected men.[109]

Unilateral or bilateral clinical varicocele is associated with defective endocrine and exocrine testicular and epididymal functions, manifested by disordered semen parameters include asthenozoospermia, teratozoospermia, oligozoospermia and azoospermia. Several studies have shown testicular endocrine abnormalities in infertile men with varicocele, marked by low serum inhibin B levels and low serum testosterone, although these endocrine changes have not been reproduced in others.[110–114] Sperm dysfunction in patients with varicocele is characterized by elevated sperm DNA fragmentation index, a build-up of oxidative stress markers, inactive mitochondrial activity and abnormal acrosome reaction (Box 4).[115] Leydig cell dysfunction has been demonstrated in patients with varicocele, in correlation with a reduction in serum testosterone levels (although the levels remained within normal limits).[116] Animal studies have demonstrated reduced intratesticular testosterone, despite normal serum testosterone level, which may jeopardize the functional and proliferative activity of androgen-dependent cells along the genital ducts, such as epididymal principle cells, seminal vesicle cells and prostate cells.[117]

The pathophysiological effects of varicocele on testicular function are incompletely understood, although the rise in scrotal temperature attributed to poor venous return has been suggested to be an important mechanism. Adequate venous return is an important mechanism for testicular cooling, which is essential for the process of spermatogenesis.[118] Testicular thermal injury occurs via alterations in RNA binding proteins and DNA within the sperm, leading to an increased rate of apoptosis.[119–121] Experimental elevation of epididymal temperature enhances apoptosis and diminishes the storage capacity of this structure resulting in impaired spermiogenesis and changes in sperm count, motility and morphology.[122,123] Oxidative stress has been suggested as another major mediator of varicocele-induced testicular injury. 80% of infertile men with varicocele and 77% of men with incidental varicocele have elevated seminal ROS concentrations.[124,125] Excessive ROS generation associated with varicocele has been attributed to an increase in nitric oxide, superoxide anion and hydrogen peroxide production, released by inducible nitric oxide synthase and xanthine oxidase in the dilated spermatic veins,[126,127] which could cause the high levels of sperm DNA damage commonly seen in patients with varicocele.[119–121,128] Oxidative stress has also been linked to a decrease in the antioxidant defense system in seminal plasma observed in varicocele.[129,130]

Some investigators suggest that varicocele causes increased hydrostatic pressure in the pampiniform plexus and venous stasis, which leads to testicular hypoperfusion and, consequently, testicular hypoxia and progressive atrophy.[131] Venous stasis also results in the insufficient removal or backflow of toxic substances from the kidney or adrenal glands. Testicular hypoperfusion and hypoxia can lead to release of vascular endothelial growth factor (VEGF) from Sertoli cells, Leydig cells, vascular endothelial cells and epididymal

Box 4 | Pathological impact of varicocele on male infertility

Testicular dysfunction
- Exocrine—impaired sperm production and increased rate of germ cell apoptosis (35–40%) resulting in oligozoospermia, teratozoospermia and azoospermia
- Endocrine—low serum inhibin and testosterone levels

Epididymal dysfunction
- Reduction in epididymal weight
- Diminished epididymal tubule diameter
- Increased rate of apoptosis of principal epididymal cells, thereby negatively affecting the process of spermiogenesis resulting in failure of sperm maturation, asthenozoospermia, and appearance of sperm with excessive cytoplasmic droplets

Sperm dysfunction
- Increased sperm DNA fragmentation index
- Build up of oxidative stress: increased ROS and reduced total antioxidant capacity
- Decreased sperm mitochondrial activity
- Loss of acrosomal integrity

principal cells,[132] which can then inhibit spermatogonial proliferation and lead to increased vascular permeability, capillary angiogenesis and thickening of basement membrane and interstitial tissue, interfering with regulation of microcirculation.[133] VEGF also causes enhanced production of nitric oxide from vascular endothelial cells perpetuating the oxidative stress in men with varicocele. VEGF is overexpressed in the epididymis of patients with varicocele, raising suspicion of its role in varicocele-associated defective spermiogenesis.[134] Larger varicoceles (grade II and III) are associated with a higher incidence of testicular growth arrest[135] and higher levels of oxidative stress markers.[130,136,137] Nevertheless, no significant correlation has been demonstrated between varicocele grade and the severity of semen quality impairment.[138]

Varicoceles can be repaired by percutaneous sclerotherapy or ligation of testicular veins (via either open microscopic or laparoscopic surgery). Radiologic embolization of varicose veins can be considered for recurrent varicocele. The impact of varicocele repair on male fertility has been assessed in many retrospective and prospective studies. A recent meta-analysis reported that varicocele repair—whether by microsurgical varicocele vein ligation, macroscopic open inguinal procedure, laparoscopic vein ligation or embolization of the varicocele veins—can significantly improve sperm count, sperm progressive motility and sperm ultrastructure.[139] Moreover, varicocele repair can enhance sperm function through reduction in oxidative stress markers and DNA fragmentation index.[139] Nevertheless, this meta-analysis failed to show significant improvement in spontaneous pregnancy rates after repair. Previous Cochrane meta-analyses have also failed to demonstrate improved paternity rates.[140,141] Marmar *et al.*,[142] on the other hand, reported a significant improvement in pregnancy rate, which has been attributed to the inclusion of men with varicocele who were normospermic or had subclinical varicocele, a high patient dropout rate resulting in loss of paternity information, limited period of follow-up after repair, inclusion of prospective and observational studies in the same meta-analysis, and heterogeneity between studies. Future prospective studies are certainly required to critically assess the effect of varicocele repair on pregnancy rate, taking into account all these confounding factors.

Hydrocele

Hydrocele is an abnormal collection of fluid between the parietal and visceral layers of the tunica vaginalis. It is the most common cause of painless scrotal swelling[143] with an incidence of 1–3% in full-term infants[144] and up to 30% in premature infants and those with delayed testicular descent. The incidence in adult males is approximately 1%,[145–147] although prevalence varies according to country. Hydroceles are bilateral in approximately 7–10% of affected men.[148] The imbalance between fluid production and absorption through tunical mesothelial cells is the underlying mechanism that is responsible for the formation of hydroceles. Hydroceles are classified as communicating or noncommunicating based on the patency of the processus vaginalis—a peritoneal pouch that invades and migrates with the gubernaculum to provide the potential space for the testis to descend into the scrotum.[149] The processus vaginalis normally closes after complete descent of the testis, within 18 months of birth. However, autopsy findings suggest that a patent processus vaginalis is present in 80–94% of infants and in 15–30% of adults.[150–153] In the presence of a unilateral patent processus vaginalis, the incidence of a contralateral patent processus vaginalis has been found to be 15–22%.[154] Hydrocele constitutes the third most common ultrasonographically-detected scrotal abnormality after varicocele and epididymal cyst.[155]

Communicating hydroceles occur when the processus vaginalis is persistently patent. They are commonly diagnosed in the pediatric age group and are frequently associated with indirect inguinal hernia when the patent processus vaginalis is wide. Diurnal variation in the size of hydrocele occurs owing to gravity-induced movement of the peritoneal fluid.[154] Although communicating hydroceles are less common in adults, they are sometimes observed in patients with a patent processus vaginalis accompanied by increased intra-abdominal fluid or pressure owing to shunts, peritoneal dialysis, or ascites.[144,154,156] Adults with connective tissue disorders have a high risk of communicating hydrocele owing to attenuation of tissue support to the inguinal openings.[144] Intrauterine exposure to polybrominated biphenyl, a brominated flame retardant and endocrine disruptor, is a risk factor for pediatric hydrocele.[157] Closure of the processus vaginalis results in a noncommunicating hydrocele. Depending on location, noncommunicating hydroceles are referred to as simple scrotal hydrocele (limited to the area surrounding the testis) or hydrocele of the cord (surrounding an isolated part of the spermatic cord). Noncommunicating hydroceles are more common in adults than children. Primary adult hydrocele is usually of idiopathic etiology, whereas secondary hydrocele can be caused by testicular torsion, tumor, infection, trauma or varicocelectomy.[158]

Scrotal hydrocele is frequently identified in infertile men by clinical examination and scrotal ultrasonography. Hussein *et al.*[159] detected hydrocele in 16.7% of infertile men, compared to 8.7% of men in a control group of fertile men.[159] Dandapat *et al.*[160] reported a similar trend whereas Palep found hydrocele in 10.43% of infertile men.[161] Pierik *et al.*[155] noted that the incidence of hydrocele in infertile men is 3.2%.

The effect of hydrocele on testicular function and spermatogenesis has been examined recently; however, a cause and effect relationship has not been confirmed in well-designed long-term studies, and no study has analyzed the improvement of fecundity rate after hydrocele repair. The impact of hydrocele on testicular geometry and size, spermatogenesis, scrotal temperature and testicular blood flow dynamics has been evaluated. Dandapat *et al.*[160] assessed the pressure effect of hydroceles in 120 men with unilateral idiopathic hydrocele, finding no pressure effect in 70% of men, testicular flattening in 22% of the cohort and pressure-induced testicular atrophy in 8% of patients. Turgut *et al.*[162] noted time-related testicular size declines in patients with hydrocele and described a rounding rather than flattening effect of hydrocele on testicular shape.[162] By contrast, Mihmanli *et al.*[148] found that testicular volume was larger in men with hydrocele and that the testis returned to normal size after hydrocele excision. They propose that this increase in size is due to hydocele pressure-induced obstruction in the vessels of the testis, which creates stasis in the venous and lymphatic outflow resulting in testicular vascular edema.[148] Some investigators have shown that hydrocele can affect spermatogenesis, which may be partially or totally absent.[160,163–165] For example, Dandapat *et al.*[160] report normal spermatogenesis in 82% of the cohort, partial arrest of spermatogenesis in 10% and a total arrest in 8%.[160] The possible pathophysiologic mechanisms that underly impaired spermatogenesis include the pressure effect of the hydrocele on the testis,[162] the reaction of testicular cells to the highly proteinaceous fluid, and raised intrascrotal temperature.[148]

The hydrostatic pressure of a hydrocele exceeds the pressure in blood vessels within the scrotum,[166] which interferes with arterial blood flow and might have an ischemic effect on the testicle. Histopathologic testicular changes observed in patients with hydrocele include interstitial fibrosis, thickening of the basement membrane, and disorganization of spermatogenic cells.[160,163–165] Testicular blood flow dynamics reveal an increase in the resistive index of the subcapsular arteries of the ipsilateral testis, compared to those in the normal testis. Mihmanli *et al.*[148] used color Doppler ultrasonography to assess blood flow before and after surgical excision of hydrocele, and found that a high-resistance flow in the intratesticular arteries before surgery was replaced by a low-resistance flow after hydrocele repair and elimination of the pressure. Nye *et al.*,[167] on the other hand, observed a lack of testicular diastolic flow ipsilateral to the hydrocele. Altered blood flow dynamics clearly indicate that hydrocele causes an ischemic insult to testicular tissue. Besides that, hydrocele repair may inadvertently injure the epididymis and vas deferens.[168]

The evidence described above suggests that pediatric and adult hydroceles are associated with male infertility, although it is important to note that some authors attribute this correlation to overuse of ultrasonography in the diagnosis of male infertility. Others believe that the psychological and emotional impact of hydrocele can also cause sexual dysfunction. Certainly, controlled randomized trials are required to prove or disapprove such a relationship and to verify the usefulness of hydrocele repair for improving paternity rates in infertile men.

Epididymal cysts

The epididymis is a narrow tightly coiled tubule (3–4 m in length) that connects the efferent ductules to the vas deferens. It is attached to the posterolateral surface of the testis, and divided into three major parts: the globus major (also known as the head or caput), the corpus (body) and the globus minor (tail or cauda). The epididymis is responsible for sperm maturation, transport and storage, and is a target for inflammation (acute or chronic) and neoplastic diseases (benign or malignant).

Epididymal cysts are the most common epididymal mass, occurring in 20–40% of asymptomatic men.[169] 75% of epididymal cysts are true cysts, meaning they are lined with epithelial cells and contain lymphatic fluid. The remaining are spermatoceles, commonly formed from obstruction of the efferent ductal system, which leads to cystic dilatation with fluid containing spermatozoa, lymphocytes, and cellular debris. True epididymal cysts can arise throughout the epididymis before and after puberty whereas spermatoceles almost always occur in the epididymal head of postpubertal men.[170] The two types are indistinguishable on ultrasonography, so the only means of differentiating epididymal cysts from spermatoceles is aspiration of the cystic fluid to assess for the presence of sperm.[171]

The exact etiology of epididymal cysts is unknown; however, Wollin *et al.*[172] have suggested they arise from vestigial remnants of the epididymis that no longer communicate with epididymal tubules.[172] Cysts have been linked to diethylstilbestrol exposure, testicular dysgenesis syndrome and cryptorchidism. Because the epididymis is an androgen-dependent structure, it has been assumed that fetal exposure to diethylstilbestrol, dietary ingestion of phytestrogen and cannabis intake have a role in causing not only epididymal cyst but also other genital anomalies, such as hypospadias and undescended testicles.[173,174] Others have hypothesized that vasal or epididymal obstruction leads to epididymal congestion, swelling and secondary cyst formation,[175] although direct measurement of hydrostatic pressure in the epididymis after vasectomy does not support this theory. Epididymal cysts can occur in association with genetic syndromes such as von Hippel–Lindau and cystic fibrosis.[169] The etiology of spermatocele is also unknown, but is thought to be the result of a focal weakening of the external layer of an epididymal tubule, leading to formation of diverticula.

The clinical significance of epididymal cysts and spermatoceles, as well as their association with male

infertility has not yet been resolved.[155] Spermatoceles have been described as 'sperm retrieval reservoirs' in men with obstructive azoospermia[176] but there have been no reports of a correlation between epididymal cysts and male infertility, even in those with bilateral epididymal cysts. Watchful waiting with regular follow-up has been suggested for both epididymal cyst and spermatocele, as long as they are small in size and produce no symptoms. Cyst excision and spermatocelectomy are recommended for abnormally large and painful lesions, although surgery is not without complications. Epididymal injury is a primary concern during excision surgery and has been diagnosed or suggested in 17–50% of patients who undergo spermatocelectomy.[168,177] Such injury can lead to epididymal obstruction.[177] Additional postoperative complications are those typical of scrotal surgery, including hematoma, hydrocele, hematocele, infection and testicular atrophy due to vascular injury. Kauffman *et al.*[178] suggested the use of microscopic surgery to reduce the incidence of injury to the epididymis, especially during spermatocelectomy.[178] Percutaneous aspiration and sclerotherapy have been attempted but are not advocated due to the risk of epididymal obstruction, chemical epididymitis and recurrence.[179]

Disorders of the seminal duct

Congenital absence of the vas deferens

The vas deferens is a paired tubular structure that extends from the tail of the epididymis into the pelvis through the inguinal canal toward the base of the bladder. At the internal ring, the vasa deferentia curve laterally and then pass medially and downward into the pelvis to join seminal vesicles to form ejaculatory ducts. The human vasa deferentia have a total capacity of 0.45 ml, which accounts for roughly 10% of the volume of normal ejaculate.[180]

Congenital absence of the vas deferens (vasal agenesis) is frequently described in men presenting with infertility. Agenesis can be partial or complete, unilateral or bilateral, and can be associated with hypoplasia of the epididymis. Embryologically, the vasa deferentia arise from the Wolffian duct, which forms in the seventh week of gestation. Fetal insult can lead to aplasia of the vas deferens.[181–183] Another well known cause of unilateral or bilateral vasal aplasia is cystic fibrosis.[184] Inheritance of a mutated cystic fibrosis transmembrane conductance regulator (*CFTR*) gene can cause secondary atresia of one or both vasa deferentia during embryogenesis. However, not all men with congenital absence of the vas deferens have cystic fibrosis.[181] Recent reports estimate that up to 99% of patients with congenital bilateral absence of the vasa deferentia (CBAVD)[184,185] and approximately 43% of men with unilateral absence of the vas deferens[186–188] will have at least one detectable *CFTR* gene mutation. Patients with vasal agenesis and concurrent renal anomalies do not typically have any mutations on cystic fibrosis gene analysis.[188] Genetic counseling and testing for *CFTR* gene mutations should be offered to men who have unilateral absence of the vas deferens and normal kidneys or bilateral absence of the vas deferens or bilateral seminal duct abnormalities. If the results are negative and renal anatomy has not been defined, abdominal ultrasonography should be performed. Findings may range from unilateral absence of the vas deferens with ipsilateral absence of the kidney, to bilateral vasal abnormalities and renal abnormalities, such as pelvic kidney.

CBAVD is found in 1.3% of men who present for fertility evaluation;[189,190] 4.4–17.0% of men with azoospermia[191] and 25% of men with obstructive azoospermia.[192] Patients with CBAVD display a spectrum of abnormalities including preserved caput epididymis, which is generally accompanied by a portion of the corpus or cauda, and absent or abnormal seminal vesicles.[193] The testes are usually normal in both size and function (androgen secretion and spermatogenesis).[194] Generally, patients are azoospermic and have acidic low-volume (<1 ml) semen, with low levels of fructose (seminal vesicular origin) and α-glucosidase (epididymal origin).[193] Physical examination (at room temperature) can confirm the bilateral absence of scrotal vasa deferentia. Men with CBAVD must use assisted reproductive technology to conceive. The standard therapeutic strategy is sperm retrieval, via testicular sperm extraction or microsurgical epididymal sperm aspiration, followed by ICSI.[195] Pregnancy rates are not notably affected by presence of a *CFTR* mutation in the male partner.[188,196] The female partner should be offered genetic analysis to test for *CFTR* mutations before proceeding with treatments that utilize the sperm of a man with CBAVD.[197]

Approximately 1% of men have unilateral vasal agenesis. These men are usually fertile because they have single patent vas deferens,[198,199] but they are at a higher risk of infertility than the general population because they have a solitary functioning testis. Unilateral vasal agenesis is most commonly encountered as an incidental finding in the vasectomy clinic or during herniotomy. 79% of patients with congenital unilateral absence of the vas deferens have ipsilateral renal agenesis,[182] and up to 90% have aplasia of the ipsilateral seminal vesicle. Approximately 20% of affected men have aplasia of the contralateral seminal vesicle and atresia of the ampullary portion of the contralateral vas deferens.[200] Therefore, a subset of men with unilateral vasal agenesis have azoospermia or other abnormal semen parameters owing to abnormalities in the contralateral derivatives of the Wolffan duct. Specifically, this condition should be referred to as unilateral intrascrotal vas deferens aplasia, because the distal parts of the contralateral vas deferens are inaccessible to palpation. Affected men have high incidence of *CFTR* gene mutations.[195] Transrectal ultrasonography (TRUS) may be useful to evaluate the ampullary portion of the contralateral vas deferens and the seminal vesicles.[200] Obstructive azoospermia in these men is treated by testicular or epididymal sperm retrieval techniques and IVF or ICSI after the female partner has been screened for *CFTR* mutations and the couple have received thorough genetic counseling.

Ejaculatory duct obstruction

Ejaculatory duct obstruction (EDO) is an uncommon but easily correctable cause of male infertility.[201] First

described in 1973, EDO is now thought to affect 1–5% of infertile men,[202] and can arise from either acquired or congenital causes. Acquired causes include trauma, inflammation, calculus formation and infection. Congenital abnormalities include atresia, stenosis, and genetic abnormalities as well as Müllerian, utricular and Wolffian cysts. Infertility is the first symptom of ejaculatory obstruction in many men, but other symptoms include decreased ejaculate force, pain during ejaculation, hematospermia, perineal or testicular pain, or prostatitis-like symptoms.[203] On physical examination, men with EDO typically have normal testicles, vasa deferentia, and secondary sexual development. Sometimes a mass might be palpated rectally, usually in the seminal vesicles.[204] Although the width and length of seminal vesicles do not generally differ between fertile and infertile men, patients with EDO tend to display cystic dilation of seminal vesicles (>15 mm transverse diameter is considered abnormal).[204] However, a clear diagnosis cannot be made without further diagnostic tests to evaluate any other sources of infertility that might be present. On semen analysis, men with EDO often demonstrate low-volume ejaculate, azoospermia or oligozoospermia, negative or very low fructose content, and low or absent sperm motility.[205] Decreased ejaculate volume (<1 ml) does not provide a clear diagnosis of EDO, and no reliable diagnostic criteria are available for partial EDO.[206]

Once a man has been initially diagnosed with complete EDO, transrectal ultrasonography with guided aspiration of dilated or cystic ejaculatory ducts or seminal vesicles is undertaken to look for sperm. If sperm are found, then surgical endoscopic relief of the obstruction by transurethral resection of ejaculatory ducts (TURED) is considered. When no sperm are detected, vasotomy and vasography are performed to visualize the anatomy of the seminal vesicles, ejaculatory ducts and distal vasa deferentia to exactly delineate the site of obstruction and whether there is any associated atresia or stenosis in the distal vas deferens. If sperm are identified in the vasal aspirate, endoscopic relief of EDO is generally performed. In the absence of vasal sperm, microsurgical epididymal sperm aspiration without EDO repair is recommended.[207]

Cystic lesions of the prostate

Widespread implementation of imaging techniques such as TRUS and endorectal MRI has increased the detection of cystic lesions of the prostate, which are thought to affect 0.5–7.9% of men.[208–210] Various methods of classifying prostatic cysts have been reported, such as whether they are congenital or acquired, or based on their position within the prostate (midline, paramedian or lateral). Most recently, Galosi *et al.*[211] suggested a new model based upon anatomical site, embryological origin and pathological characteristics that classifies cysts into six major types (Box 5). A detailed description of these subtypes is outside the scope of this article, but there are two types of cyst (midline prostatic cysts and ejaculatory duct cysts) that can obstruct the ejaculatory ducts and lead to male infertility, and these will be discussed further.

Box 5 | Classification of prostatic cysts

- Midline cysts: cysts of the prostatic utricle (previously known as cysts of the Müllerian duct), cystic dilatation of prostatic utricles, enlarged prostatic utricles
- Cysts of the ejaculatory duct
- Cysts of the parenchyma
- Complicated cysts
- Cystic tumors
- Cysts secondary to other disease

Midline prostatic cysts can be divided into three types: prostatic utricle cysts (previously called Müllerian duct cysts), cystic dilatation of the prostatic utricle and enlarged prostatic utricles. A prostatic utricle cyst results from failure of the Müllerian ducts to regress causing focal saccular dilatation.[212] Located at the region of the verumontanum, these cysts may extend above the prostate or slightly lateral to the midline, and may grow into a large mass. Prostatic utricle cysts do not communicate with the urethra, therefore aspirations do not contain spermatozoa.[213] This type of cyst affects 5% of men with obstructive azoospermia.[214] The condition is usually asymptomatic, but patients in the third or fourth decade of life[215] may develop irritative and obstructive urinary symptoms as well as hematuria, hematospermia, bloody urethral discharge, ejaculatory pain, urinary tract infection, epididymitis, infertility and constipation.[216] Cystic dilatation of the prostatic utricle (cystic utricle) arises due to obstruction of the junction between the utricle and the urethra.[213,217] Such cysts are therefore able to communicate with the posterior urethra.[215] Typically, cystic utricles are smaller than prostatic utricle cysts, are strictly localized to the midline, and measure no more than 15 mm (along the longest axis). Both prostatic utricle cysts and cystic utricles can enlarge and compress both ejaculatory ducts resulting in altered semen parameters, and sometimes azoospermia. The third type of midline prostatic cyst is not technically a cyst but rather an enlarged or hypertrophied prostatic utricle that communicates freely with the prostatic urethra. Mainly detected in children and adolescents, enlarged prostatic utricles are frequently found in children with urogenital malformations, such as proximal hypospadias or virilization defects.[218] TRUS and cystourethrography usually reveal an enlarged prostatic utricle that is midline and posterior—the wide opening into the posterior urethra can be easily identified. This type of cyst does not typically obstruct the ejaculatory ducts.[212]

Ejaculatory duct cysts originate from the Wolffian ducts and occupy a paramedian or median position in the prostatic gland above the level of the verumontanum.[211] Such cysts can be congenital or acquired, with etiologies including partial distal obstruction caused by chronic infection, transurethral manipulation, tuberculosis or urethral foreign body.[219] Ejaculatory duct cysts can be unilateral or bilateral and are associated with obstructive azoospermia. When small, these cysts appear on TRUS as intraprostatic masses just lateral to

the midline at the base and midline at the level of the verumontanum.[215] When large, however, these lesions can mimic cystic utricles and prostatic utricle cysts. Clinical presentation depends on the size of the cyst; small cysts are usually asymptomatic while large ones can cause hematospermia, ejaculatory pain, azoospermia and male infertility.[215,220] Diagnostic work-up includes TRUS and ultrasonography-guided transperineal aspiration of cystic fluid to detect the presence of sperm.[211]

On TRUS, most midline prostatic cysts and ejaculatory duct cysts appear as simple oval or rounded anechoic cysts or complex echogenic cysts, making radiological differentiation impossible. Diagnostic aspiration can aid differential diagnosis—detection of sperm in the cystic fluid aspirate excludes the possibility of a prostatic utricle cyst. Utilization of MRI of the pelvis with a rectal coil is preferred in conditions when the information obtained by TRUS is not satisfactory.[221,222] Treatment of midline prostatic cyst and ejaculatory duct cyst depends on the cyst size and its clinical effects. Because most cysts are small and asymptomatic, generally no treatment is required.[223] However, cysts that cause hematospermia, low semen volume, abnormal semen parameters, infertility, urine retention, rectal discomfort and urinary tract infections should be treated. There are several treatment options, including simple transrectal aspiration, sclerotherapy of the cyst under TRUS guidance, open surgical removal, TURED, and endoscopic incisional deroofing of the cyst (marsupialization).[223] These treatments usually result in appearance of sperm in the ejaculate and improve patient's symptoms.

Polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common congenital kidney disease that urologists encounter in clinical practice, with an incidence in the general population of 0.0010–0.0025%.[224,225] Approximately 600,000 Americans are affected,[226] and about 95% of individuals with ADPKD have an affected parent (5% have a *de novo* mutation).[227] ADPKD is an autosomal dominant disease that is attributed to mutations in three polycystin genes, *PKD1*, *PKD2* and *PKD3*. The condition is characterized by gradual and progressive development of cysts in the kidney parenchyma, which will eventually occupy the entire kidney. Cysts can arise from any portion of the kidney tubules and increase in number and size with age. Affected patients are likely to be asymptomatic before the age of 30 years, but ultrasonography may reveal the presence of cysts. From age 30–40 years, the manifestation of symptoms occurs—palpable kidneys, microscopic or gross hematuria, urinary tract infection, flank pain, or renal colic from passing clots. Gradual elevation of serum creatinine typically begins at 40–50 years of age and the patient may require a kidney transplant after the age of 50 years.[228] Extrarenal cyst development has been described in the liver, pancreas, and arachnoid mater, as well as structures of the male reproductive tract including the epididymis, seminal vesicles, prostate and ejaculatory ducts.[229]

Although it was previously thought that men with ADPKD were not at increased risk of infertility, recent reports on a limited number of patients suggest otherwise. Torra *et al.*[230] performed a study on 22 men with ADPKD and detected semen abnormalities in 20 individuals; asthenospermia was the most common finding.[230] Another study found necrospermia to be the most common semen abnormality.[231] Low semen volume, oligospermia and teratospermia have also been reported.[230] Several mechanisms of male infertility and abnormal semen parameters in ADPKD have been postulated. The presence of cysts in the seminal vesicles or ejaculatory ducts could cause obstruction of semen outflow or pathological dilatation and necrospermia.[231–233] Alternatively, Handelsman *et al.*[234] suggest that disruption of the hypothalamic–pituitary–gonadal axis due to uremia might cause consequent testicular failure.[234]

ADPKD is a form of ciliopathy that results from synthesis of abnormal polycystins, which are important ciliary proteins. Proteomic studies on normal eukaryotic flagellum revealed that polycystin-1 (the product of *PKD1*, mutated in 80–90% of patients with ADPKD) and polycystin-2 (the product of *PKD2*, responsible for the other 10–15%), are co-localized in the basal body, axoneme and plasma membranes of cilia and flagellum,[235] which suggests they may function as a receptor–channel complex that responds to specific stimuli and induces signal transduction.[236] Polycystins also have important roles in axonemal microtubule assembly and function.[235,237] The axonemes of normal sperm flagellum and motile cilia of the body contain the common ciliary pattern of two central microtubule doublets surrounded by nine peripheral microtubule doublets (known as 9+2). In some patients with ADPKD this pattern is changed to (9+0), which renders the sperm immobile or even dead.[238,239] Furthermore, a recent report showed that sperm lacking central microtubules fail to fertilize the ovum during IVF or ICSI, which suggests that the central microtubules may have a role in fetal development.[238]

The protein encoded by *PKD2* (polycystin-2, a calcium ion channel) may have an important role in male infertility. Animal studies in *Drosophila* reported that polycystin-2 is present in both the tail and head region that contains the acrosome of sperm. Targeted disruption of the *PKD2* gene in *Drosophila* causes male sterility without affecting spermatogenesis. The sperm are motile, but cannot swim into the reproductive tract of the female. This suggests that *Drosophila* polycystin-2 operates in the directional movement of sperm inside the female genital tract.[240] Another study on sea urchin sperm confirmed the localization of a polycystin-2 homolog in the head of sperm and demonstrated its role in inducing acrosome reaction probably because it can facilitate the entry of calcium.[241] The function of polycystin-2 in human sperm has not yet been verified.[238]

The association between ADPKD and male factor infertility remains unresolved. Large prospective controlled studies are needed to examine the frequency and prevalence of male factor infertility among patients with

ADPKD. In addition, more-sophisticated molecular studies are needed in infertile men with ADPKD and immotile sperm. For example, proteomics of human sperm flagellum might be useful to elucidate the exact defects.

Inguinal hernia

Inguinal hernia repair is one of the most common surgical procedures reported in Western countries, estimated to be performed in 5% of the general population.[242] Over 700,000 inguinal hernia operations are performed every year in the US alone.[243] Inguinal hernias are more common in men, and most frequently occur during infancy.[244] Genetic studies have linked several mutations to increased incidence of inguinal hernia with male infertility. Ribarski *et al.*[245] found that a mutation in the *USP26* gene (1090C>T) was associated with inguinal hernia in infertile men.[245] Several diseases that affect connective tissue, including Marfan syndrome[246] and other genetic syndromes, may manifest as inguinal hernia and male infertility. For example, 76% of patients with androgen insensitivity syndrome and 80–90% of patients with persistent Müllerian duct syndrome present with inguinal hernia.[245,247]

Surgical repair of hernia in both children and adults can also affect fertility. Pediatric hernia repair may be complicated by testicular atrophy (1–2%), injury to the vas deferens (0.13–1.60%), iatrogenic cryptorchidism (0.6–2.9%)[248] or autoimmune orchitis (0.8–1.4%).[249,250] Although some surgeons prefer to use contralateral inguinal exploration to repair potential patent processus vaginales in children <2 years old,[251] most surgeons no longer advocate this approach. The reluctance to perform bilateral exploration is attributed to the high risk of testicular atrophy (2–30%)[252] and bilateral vasal obstruction (up to 40%).[253] Adult inguinal hernia repairs can be described as tension or tension-free; tension repairs involve use of the patient's own tissues while tension-free repairs incorporate prosthetic mesh.[254] Approximately 75–80% of adult hernia operations involve the placement of mesh via either open or laparoscopic surgery.[243] Tension repairs often incorporate aponeuroses from the abdominal muscles for complex reconstruction of the inguinal canal. Using a patient's own tissues for inguinal hernia repair can be beneficial to younger patients, for whom meshes can prove harmful.[254] This technique also requires no special materials or operating room equipment, and can be done with minimum preparation. Currently, open tension-free inguinal herniorrhaphy, also called Lichtenstein onlay mesh repair, is the most common surgical technique. Lichtenstein first introduced the technique in 1986, which entails the use of nonabsorbable sutures and prosthetic mesh to reinforce the inguinal canal floor.[255] Another tension-free technique that is currently used to repair inguinal hernia is the prolene hernia system,[256] which consists of polypropylene mesh that has an onlay patch, a connector and underlay patch.

The use of polypropylene mesh in bilateral hernia repair can lead to infertility owing to vasal injury and consequently obstructive azoospermia.[243] The incidence of obstructive azoospermia after hernia repair has been reported at 0.3% in adults.[257] Two mechanisms of injury to the genital tract can occur during herniorrhaphy—transection and compression.[242] Transection injury is responsible for about 25% of injuries to the vasa deferentia incurred during hernia repair. This type of injury can be recognized during surgery, allowing immediate reconstruction. Compression injury, on the other hand, usually presents much later. Compression might be caused by the handling of vasa deferentia during surgery, by the mesh itself, or by delayed fibrosis around the mesh.[242] Genital tract obstruction after herniorrhaphy has also been shown to increase antisperm antibodies that can further diminish spermatogenesis.[258]

Conclusions

Diagnosis and treatment of physical abnormalities related to male infertility is an important task that should be undertaken not only by the urologist or andrologist who provides care to the infertile man but also by the pediatrician, medical internist, general surgeon and radiologist who come across these abnormalities in their practice. Protecting the fertility potential in men with these abnormalities, which may appear during various developmental periods from infancy to adulthood, and selecting the least harmful form of therapy can ensure better quality of life and lower the risk of childlessness.

The exact relationships between some of these abnormalities and male infertility are incompletely understood and uncertainties still surround the efficacy of therapies to improve male fertility potential. Elucidation of these missing data requires the institution of properly designed prospective controlled studies to examine the advantages and efficacy of the available treatment options. In addition, more molecular biology research is needed to provide a better understanding of the basic cellular defects underlying fertility issues in affected men. Although most of these abnormalities are treatable by surgery, an approach that combines both clinical and basic scientific research can offer the best opportunities to find the most efficacious form of surgical therapy that is least damaging to male reproductive function. Furthermore, surgical procedures might be supplemented with targeted molecular therapy in the future.

Review criteria

Data on the role of various physical deformities in male infertility were extensively searched through PubMed, Scopus, Science direct and Ovid Medline using the exploding option. The keywords used in the search included "male infertility", "semen analysis" and the specific term for each physical abnormality. Relevant articles from 1988 to 2011 were identified. Cross-references were checked in each of the studies, and relevant articles retrieved. Articles in English language were carefully reviewed; while only the abstracts of articles in other languages were examined.

1. Lee, P. A. Consequence of cryptorchidism: relationship to etiology and treatment. *Curr. Probl. Pediatr.* **25**, 232–236 (1995).
2. Tomiyama, H. *et al.* Testicular descent, cryptorchidism and inguinal hernia: the Melbourne perspective. *J. Pediatr. Urol.* **1**, 11–25 (2005).
3. Berkowitz, G. S. *et al.* Prevalence and natural history of cryptorchidism. *Pediatrics* **92**, 44–49 (1993).
4. Scorer, C. G. The descent of the testis. *Arch. Dis. Child* **39**, 605–609 (1964).
5. Barthold, J. S. & Gonzalez, R. The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy. *J. Urol.* **170**, 2396–2401 (2003).
6. Acerini, C. L., Miles, H. L., Dunger, D. B., Ong, K. K. & Hughes, I. A. The descriptive epidemiology of congenital and acquired cryptorchidism in a UK infant cohort. *Arch. Dis. Child* **94**, 868–872 (2009).
7. Boisen, K. A. *et al.* Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. *Lancet* **363**, 1264–1269 (2004).
8. Cortes, D., Kjellberg, E. M., Breddam, M. & Thorup, J. The true incidence of cryptorchidism in Denmark. *J. Urol.* **179**, 314–318 (2008).
9. Kumanov, P., Tomova, A., Robeva, R. & Hubaveshki, S. Prevalence of cryptorchidism among Bulgarian boys. *J. Clin. Res. Pediatr. Endocrinol.* **1**, 72–79 (2008).
10. Ghazzal, A. M. Inguinal hernias and genital abnormalities in young Jordanian males. *East Mediterr. Health J.* **12**, 483–488 (2006).
11. Virtanen, H. E., Rajpert-De Meyts, E., Main, K. M., Skakkebaek, N. E. & Toppari, J. Testicular dysgenesis syndrome and the development and occurrence of male reproductive disorders. *Toxicol. Appl. Pharmacol.* **207** (2 Suppl.), 501–505 (2005).
12. Sijstermans, K., Hack, W. W., Meijer, R. W. & van der Voort-Doedens, L. M. The frequency of undescended testis from birth to adulthood: a review. *Int. J. Androl.* **31**, 1–11 (2008).
13. Lee, P. A. Fertility in cryptorchidism. Does treatment make a difference? *Endocrinol. Metab. Clin. North Am.* **22**, 479–490 (1993).
14. Wilkerson, M. L., Bartone, F. F., Fox, L. & Hadziselimovic, F. Fertility potential: a comparison of intra-abdominal and intracanalicular testes by age groups in children. *Horm. Res.* **55**, 18–20 (2001).
15. Mieusset, R. *et al.* Increase in testicular temperature in case of cryptorchidism in boys. *Fertil. Steril.* **59**, 1319–1321 (1993).
16. Zhang, X. S. *et al.* Activation of extracellular signal-related kinases 1 and 2 in Sertoli cells in experimentally cryptorchid rhesus monkeys. *Asian J. Androl.* **8**, 265–272 (2006).
17. Liu, Y. & Li, X. Molecular basis of cryptorchidism-induced infertility. *Sci. China Life Sci.* **53**, 1274–1283 (2010).
18. Hadziselimovic, F., Hocht, B., Herzog, B. & Buser, M. W. Infertility in cryptorchidism is linked to the stage of germ cell development at orchidopexy. *Horm. Res.* **68**, 46–52 (2007).
19. Zivkovic, D., Bica, D. T. & Hadziselimovic, F. Relationship between adult dark spermatogonia and secretory capacity of Leydig cells in cryptorchidism. *BJU Int.* **100**, 1147–1149 (2007).
20. Cicigoi, A. & Bianchi, M. Seminal duct abnormalities in cryptorchism: our experience with 334 cases [Italian]. *Arch. Ital. Urol. Nefrol. Androl.* **63**, 107–111 (1991).
21. Favorito, L. A., Costa, W. S. & Sampaio, F. J. Analysis of anomalies of the epididymis and processus vaginalis in human fetuses and in patients with cryptorchidism treated and untreated with human chorionic gonadotropin. *BJU Int.* **98**, 854–857 (2006).
22. Chilvers, C., Dudley, N. E., Gough, M. H., Jackson, M. B. & Pike, M. C. Undescended testis: the effect of treatment on subsequent risk of subfertility and malignancy. *J. Pediatr. Surg.* **21**, 691–696 (1986).
23. Hadziselimovic, F. & Herzog, B. The importance of both an early orchidopexy and germ cell maturation for fertility. *Lancet* **358**, 1156–1157 (2001).
24. Chung, E. & Brock, G. B. Cryptorchidism and its impact on male fertility: a state of art review of current literature. *Can. Urol. Assoc. J.* **5**, 210–214 (2011).
25. van der Steeg, J. W. *et al.* Role of semen analysis in subfertile couples. *Fertil. Steril.* **95**, 1013–1019.
26. Lee, P. A. & Coughlin, M. T. The single testis: paternity after presentation as unilateral cryptorchidism. *J. Urol.* **168**, 1680–1682 (2002).
27. Coughlin, M. T. *Cryptorchidism and male fertility: a study of the determinants of infertility. Among formerly cryptorchid and control men*. Thesis, University of Pittsburgh (2004).
28. Kolon, T. F., Patel, R. P. & Huff, D. S. Cryptorchidism: diagnosis, treatment, and long-term prognosis. *Urol. Clin. North Am.* **31**, 469–480 (2004).
29. Lee, P. A. *et al.* Paternity after bilateral cryptorchidism. A controlled study. *Arch. Pediatr. Adolesc. Med.* **151**, 260–263 (1997).
30. Ritzen, E. M. *et al.* Nordic consensus on treatment of undescended testes. *Acta Paediatr.* **96**, 638–643 (2007).
31. Lee, P. A. Fertility after cryptorchidism: epidemiology and other outcome studies. *Urology* **66**, 427–431 (2005).
32. Haimov-Kochman, R., Prus, D., Farchat, M., Bdolah, Y. & Hurwitz, A. Reproductive outcome of men with azoospermia due to cryptorchidism using assisted techniques. *Int. J. Androl.* **33**, e139–e143 (2010).
33. Shin, D., Lemack, G. E. & Goldstein, M. Induction of spermatogenesis and pregnancy after adult orchiopexy. *J. Urol.* **158**, 2242 (1997).
34. Cassorla, F. G. *et al.* Testicular volume during early infancy. *J. Pediatr.* **99**, 742–743 (1981).
35. Schonfeld, W. A. & Beebe, G. W. Normal growth and variation in the male genitalia from birth. *J. Urol.* **48**, 759 (1942).
36. Bahk, J. Y., Jung, J. H., Jin, L. M. & Min, S. K. Cut-off value of testes volume in young adults and correlation among testes volume, body mass index, hormonal level, and seminal profiles. *Urology* **75**, 1318–1323 (2010).
37. Nieschlag, E. & Behre, H. M. in *Andrology: Male Reproductive Health and Dysfunction* (eds Nieschlag, E., Behre, H. M. & Nieschlag, S.) 93–100 (Springer–Verlag, Berlin, 2010).
38. Kim, H. & Goldstein, M. in *Clinical Andrology* (eds Bjorndahl, L., Giwercman, A., Tournaye, H. & Weidner, W.) 112 (Informa Healthcare, London, 2010).
39. Huff, D. S., Snyder, H. M. 3rd, Hadziselimovic, F., Blyth, B. & Duckett, J. W. An absent testis is associated with contralateral testicular hypertrophy. *J. Urol.* **148**, 627–628 (1992).
40. Najjar, S. S., Takla, R. J. & Nassar, V. H. The syndrome of rudimentary testes: occurrence in five siblings. *J. Pediatr.* **84**, 119–122 (1974).
41. Caldwell, P. D. & Smith, D. W. The XXY (Klinefelter's) syndrome in childhood: detection and treatment. *J. Pediatr.* **80**, 250–258 (1972).
42. Dickerman Z. *et al.* Pituitary–gonadal function, pubertal development and sperm counts in cryptorchidism: a longitudinal study. *Pediat. Adolesc. Endocr.* **6**, 195–214 (1979).
43. Kass, E. J. & Belman, A. B. Reversal of testicular growth failure by varicocele ligation. *J. Urol.* **137**, 475–476 (1987).
44. Kogan, S. J. *et al*. in *Dialogues in Pediatric Urology* Vol. 7 (ed. Ehrlich, R. E.) 1–6 (William J. Miller Associates, New York, 1984).
45. Lyon, R. P., Marshall, S. & Scott, M. P. Varicocele in childhood and adolescence: implication in adulthood infertility? *Urology* **19**, 641–644 (1982).
46. Ebstein, J. I. in *Robbins and Cotran Pathologic Basis of Disease*, 7th edn (eds Kumar, V., Abbas, A. & Fausto, N) 1023–1058 (Saunders Elsevier, Philadelphia, 2004).
47. World Health Organization. *WHO laboratory manual for the examination and processing of human semen* 5th edn (WHO, Geneva, 2010).
48. Cortes, D., Muller, J. & Skakkebaek, N. E. Proliferation of Sertoli cells during development of the human testis assessed by stereological methods. *Int. J. Androl.* **10**, 589–596 (1987).
49. Zhengwei, Y., Wreford, N. G., Royce, P., de Kretser, D. M. & McLachlan, R. I. Stereological evaluation of human spermatogenesis after suppression by testosterone treatment: heterogeneous pattern of spermatogenic impairment. *J. Clin. Endocrinol. Metab.* **83**, 1284–1291 (1998).
50. Nocks, B. N. Polyorchidism with normal spermatogenesis and equal sized testes: a theory of embryological development. *J. Urol.* **120**, 638–640 (1978).
51. Mehan, D. J., Chehval, M. J. & Ullah, S. Polyorchidism. *J. Urol.* **116**, 530–532 (1976).
52. Amodio, J. B., Maybody, M., Slowotsky, C., Fried, K. & Foresto, C. Polyorchidism: report of 3 cases and review of the literature. *J. Ultrasound Med.* **23**, 951–957 (2004).
53. Singer, B. R., Donaldson, J. G. & Jackson, D. S. Polyorchidism: functional classification and management strategy. *Urology* **39**, 384–388 (1992).
54. Bergholz, R., Koch, B., Spieker, T. & Lohse, K. Polyorchidism: a case report and classification. *J. Pediatr. Surg.* **42**, 1933–1935 (2007).
55. Bostwick, D. G. in *Urologic Surgical Pathology* (eds Bostwick, D. G. & Elbe, J. N.) 647–674 (Mosby, St Louis, 1997).
56. Spranger, R., Gunst, M. & Kuhn, M. Polyorchidism: a strange anomaly with unsuspected properties. *J. Urol.* **168**, 198 (2002).
57. Hakami, M. & Mosavy, S. H. Triorchidism with normal spermatogenesis: an unusual cause for failure of vasectomy. *Br. J. Surg.* **62**, 633 (1975).
58. Ozok, G., Taneli, C., Yazici, M., Herek, O. & Gokdemir, A. Polyorchidism: a case report and review of the literature. *Eur. J. Pediatr. Surg.* **2**, 306–307 (1992).
59. Ferro, F. & Iacobelli, B. Polyorchidism and torsion. A lesson from 2 cases. *J. Pediatr. Surg.* **40**, 1662–1664 (2005).
60. Francesco, A. *et al.* Immunohistochemistry: additional armamentarium in the management of polyorchidism. *Pediatr. Int.* **50**, 586–588 (2008).
61. Shabtai, F., Schwartz, A., Hart, J., Halbrecht, I. & Kimche, D. Chromosomal anomaly and malformation syndrome with abdominal polyorchidism. *J. Urol.* **146**, 833–834 (1991).
62. Mathur, P., Prabhu, K. & Khamesra, H. L. Polyorchidism revisited. *Pediatr. Surg. Int.* **18**, 449–450 (2002).
63. Bayraktar, A. *et al.* Management of polyorchidism: Surgery or conservative management? *J. Hum. Reprod. Sci.* **3**, 162–163 (2010).

64. Ahmadnia, H. & Molaei, M. Polyorchidism in a patient with azoospermia. *Saudi J. Kidney Dis. Transpl.* **20**, 670–671 (2009).
65. Cuckow, P. M. & Frank, J. D. Torsion of the testis. *BJU Int.* **86**, 349–353 (2000).
66. Romero, F. R., Gomes, R. P., Lorenzini, F., Erdmann, T. R. & Tambara Filho, R. Ipsilateral testicular necrosis and atrophy after 1,080-degree torsion of the spermatic cord in rats. *Acta Cir. Bras.* **24**, 118–123 (2009).
67. Abber, J. C. & Lue, T. F. Extravaginal torsion of spermatic cord in adult. *Urology* **38**, 79–81 (1991).
68. Callewaert, P. R. & Van Kerrebroeck, P. New insights into perinatal testicular torsion. *Eur. J. Pediatr.* **169**, 705–712 (2010).
69. Pentyala, S., Lee, J., Yalamanchili, P., Vitkun, S. & Khan, S. A. Testicular torsion: a review. *J. Low Genit. Tract Dis.* **5**, 38–47 (2001).
70. Favorito, L. A., Cavalcante, A. G. & Costa, W. S. Anatomic aspects of epididymis and tunica vaginalis in patients with testicular torsion. *Int. Braz. J. Urol.* **30**, 420–424 (2004).
71. Osegbe, D. N. & Amaku, E. O. The causes of male infertility in 504 consecutive Nigerian patients. *Int. Urol. Nephrol.* **17**, 349–358 (1985).
72. Callewaert, P. R. & Van Kerrebroeck, P. New insights into perinatal testicular torsion. *Eur. J. Pediatr.* **169**, 705–712 (2010).
73. Thomas, W. E., Cooper, M. J., Crane, G. A., Lee, G. & Williamson, R. C. Testicular exocrine malfunction after torsion. *Lancet* **2**, 1357–1360 (1984).
74. Anderson, M. J., Dunn, J. K., Lipshultz, L. I. & Coburn, M. Semen quality and endocrine parameters after acute testicular torsion. *J. Urol.* **147**, 1545–1550 (1992).
75. Ichikawa, T., Kitagawa, N., Shiseki, Y., Sumiya, H. & Shimazaki, J. Testicular function after spermatic cord torsion [Japanese]. *Hinyokika Kiyo.* **39**, 243–248 (1993).
76. Tryfonas, G. *et al.* Late postoperative results in males treated for testicular torsion during childhood. *J. Pediatr. Surg.* **29**, 553–556 (1994).
77. Fisch, H., Laor, E., Reid, R. E., Tolia, B. M. & Freed, S. Z. Gonadal dysfunction after testicular torsion: luteinizing hormone and follicle-stimulating hormone response to gonadotropin releasing hormone. *J. Urol.* **139**, 961–964 (1988).
78. Brasso, K. *et al.* Testicular torsion: a follow-up study. *Scand. J. Urol. Nephrol.* **27**, 1–6 (1993).
79. Turner, T. T., Tung, K. S., Tomomasa, H. & Wilson, L. W. Acute testicular ischemia results in germ cell-specific apoptosis in the rat. *Biol. Reprod.* **57**, 1267–1274 (1997).
80. Turner, T. T., Bang, H. J. & Lysiak, J. J. Experimental testicular torsion: reperfusion blood flow and subsequent testicular venous plasma testosterone concentrations. *Urology* **65**, 390–394 (2005).
81. Goldwasser, B., Weissenberg, R., Lunenfeld, B., Nativ, O. & Many, M. Semen quality and hormonal status of patients following testicular torsion. *Andrologia* **16**, 239–243 (1984).
82. Taskinen, S., Taskinen, M. & Rintala, R. Testicular torsion: orchiectomy or orchiopexy? *J. Pediatr. Urol.* **4**, 210–213 (2008).
83. Romeo, C. *et al.* Late hormonal function after testicular torsion. *J. Pediatr. Surg.* **45**, 411–413 (2010).
84. Daehlin, L., Ulstein, M., Thorsen, T. & Hoisaeter, P. A. Follow-up after torsion of the spermatic cord. *Scand. J. Urol. Nephrol*. **179** (Suppl.), 139–142 (1996).
85. Rybkiewicz, M. Long-term and late results of treatment in patients with a history of testicular torsion [Polish]. *Ann. Acad. Med. Stetin*. **47**, 61–75 (2001).
86. Anderson, J. B. & Williamson, R. C. The fate of the human testes following unilateral torsion of the spermatic cord. *Br. J. Urol.* **58**, 698–704 (1986).
87. Hadziselimovic, F., Geneto, R. & Emmons, L. R. Increased apoptosis in the contralateral testes of patients with testicular torsion as a factor for infertility. *J. Urol.* **160**, 1158–1160 (1998).
88. Klotz, T., Vorreuther, R., Heidenreich, A., Zumbe, J. & Engelmann, U. Testicular tissue oxygen pressure. *J. Urol.* **155**, 1488–1491 (1996).
89. Hagen, P., Buchholz, M. M., Eigenmann, J. & Bandhauer, K. Testicular dysplasia causing disturbance of spermiogenesis in patients with unilateral torsion of the testis. *Urol. Int.* **49**, 154–157 (1992).
90. Tanyel, F. C., Buyukpamukcu, N. & Hicsonmez, A. Contralateral testicular blood flow during unilateral testicular torsion. *Br. J. Urol.* **63**, 522–524 (1989).
91. Zini, A. *et al*. Germ cell apoptosis and endothelial nitric oxide synthase (eNOS) expression following ischemia-reperfusion injury to testis. *Arch. Androl.* **41**, 57–65 (1998).
92. Shiraishi, K., Yoshida, K. & Naito, K. Activation of endothelial nitric oxide synthase in contralateral testis during unilateral testicular torsion in rats. *Arch. Androl.* **49**, 179–190 (2003).
93. Lysiak, J. J., Nguyen, Q. A., Kirby, J. L. & Turner, T. T. Ischemia-reperfusion of the murine testis stimulates the expression of proinflammatory cytokines and activation of c-jun N-terminal kinase in a pathway to E-selectin expression. *Biol. Reprod.* **69**, 202–210 (2003).
94. Akgur, F. M., Kilinc, K. & Aktug, T. Is ipsilateral testis mandatory for the occurrence of contralateral intratesticular biochemical changes indicative of hypoxia after unilateral spermatic cord torsion? *Eur. Urol.* **28**, 143–146 (1995).
95. Akgur, F. M., Kilinc, K., Tanyel, F. C., Buyukpamukcu, N. & Hicsonmez, A. Ipsilateral and contralateral testicular biochemical acute changes after unilateral testicular torsion and detorsion. *Urology* **44**, 413–418 (1994).
96. Arap, M. A. *et al.* Late hormonal levels, semen parameters, and presence of antisperm antibodies in patients treated for testicular torsion. *J. Androl.* **28**, 528–532 (2007).
97. Lysiak, J. J. The role of tumor necrosis factor-alpha and interleukin-1 in the mammalian testis and their involvement in testicular torsion and autoimmune orchitis. *Reprod. Biol. Endocrinol.* **10**, 9 (2004).
98. Fu, G. B. *et al.* Antisperm-antibodies induced by testicular torsion and its influence on testicular function [Chinese]. *Zhonghua Nan Ke Xue* **12**, 988–991 (2006).
99. Ringdahl, E. & Teague, L. Testicular torsion. *Am. Fam. Physician* **74**, 1739–1743 (2006).
100. Yin, S. & Trainor, J. L. Diagnosis and management of testicular torsion, torsion of the appendix testis, and epididymitis. *Clin. Ped. Emerg. Med.* **10**, 38–44 (2009).
101. Steeno, O., Knops, J., Declerck, L., Adimoelja, A. & van de Voorde, H. Prevention of fertility disorders by detection and treatment of varicocele at school and college age. *Andrologia* **8**, 47–53 (1976).
102. Sylora, J. A. & Pryor, J. L. Varicocele. *Curr. Ther. Endocrinol. Metab.* **5**, 309–314 (1994).
103. Green, K. F., Turner, T. T. & Howards, S. S. Varicocele: reversal of the testicular blood flow and temperature effects by varicocele repair. *J. Urol.* **131**, 1208–1211 (1984).
104. Cozzolino, D. J. & Lipshultz, L. I. Varicocele as a progressive lesion: positive effect of varicocele repair. *Hum. Reprod. Update* **7**, 55–58 (2001).
105. Marmar, J. L. The pathophysiology of varicoceles in the light of current molecular and genetic information. *Hum. Reprod. Update* **7**, 461–472 (2001).
106. Jarow, J. P. Effects of varicocele on male fertility. *Hum. Reprod. Update* **7**, 59–64 (2001).
107. Kursh, E. D. What is the incidence of varicocele in a fertile population? *Fertil. Steril.* **48**, 510–511 (1987).
108. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. *Fertil. Steril.* **57**, 1289–1293 (1992).
109. Dubin, L. & Amelar, R. D. Etiologic factors in 1294 consecutive cases of male infertility. *Fertil. Steril.* **22**, 469–474 (1971).
110. Pierik, F. H. *et al.* Increased serum inhibin B levels after varicocele treatment. *Clin. Endocrinol.* **54**, 775–780 (2001).
111. Goulis, D. *et al.* Inhibin B and anti-Mullerian hormone in spermatic vein of subfertile men with varicocele. *Reprod. Sci.* **18**, 551–555 (2011).
112. Mormandi, E. *et al.* Serum levels of dimeric and monomeric inhibins and the degree of seminal alteration in infertile men with varicocele. *Andrologia* **35**, 106–111 (2003).
113. Younes, A. K. Low plasma testosterone in varicocele patients with impotence and male infertility. *Arch. Androl.* **45**, 187–195 (2000).
114. Pirke, K. M., Vogt, H. J., Sintermann, R. & Spyra, B. Testosterone in peripheral plasma, spermatic vein and in testicular tissue under basal conditions and after HCG-stimulation in patients with varicocele. *Andrologia* **15**, 637–641 (1983).
115. Lacerda, J. I. *et al.* Adolescent varicocele: improved sperm function after varicocelectomy. *Fertil. Steril.* **95**, 994–999 (2011).
116. Hudson, R. W. Free sex steroid and sex hormone-binding globulin levels in oligozoospermic men with varicoceles. *Fertil. Steril.* **66**, 299–304 (1996).
117. Luo, D. Y., Yang, G., Liu, J. J., Yang, Y. R. & Dong, Q. Effects of varicocele on testosterone, apoptosis and expression of StAR mRNA in rat Leydig cells. *Asian J. Androl.* **13**, 287–291 (2011).
118. Goldstein, M. & Eid, J. F. Elevation of intratesticular and scrotal skin surface temperature in men with varicocele. *J. Urol.* **142**, 743–745 (1989).
119. Yin, Y., Hawkins, K. L., DeWolf, W. C. & Morgentaler, A. Heat stress causes testicular germ cell apoptosis in adult mice. *J. Androl.* **18**, 159–165 (1997).
120. Fujisawa, M., Yoshida, S., Kojima, K. & Kamidono, S. Biochemical changes in testicular varicocele. *Arch. Androl.* **22**, 149–159 (1989).
121. Nishiyama, H. *et al.* Decreased expression of cold-inducible RNA-binding protein (CIRP) in male germ cells at elevated temperature. *Am. J. Pathol.* **152**, 289–296 (1998).
122. Ozturk, U. *et al.* The effects of experimental left varicocele on the epididymis. *Syst. Biol. Reprod. Med.* **54**, 177–184 (2008).
123. Bedford, J. M. & Yanagimachi, R. Epididymal storage at abdominal temperature reduces the time required for capacitation of hamster spermatozoa. *J. Reprod. Fertil.* **91**, 403–410 (1991).
124. Sharma, R. K., Pasqualotto, F. F., Nelson, D. R., Thomas, A. J. Jr & Agarwal, A. The reactive oxygen species-total antioxidant capacity score is a new measure of oxidative stress to predict

male infertility. *Hum. Reprod.* **14**, 2801–2807 (1999).
125. Hendin, B. N., Kolettis, P. N., Sharma, R. K., Thomas, A. J. Jr & Agarwal, A. Varicocele is associated with elevated spermatozoal reactive oxygen species production and diminished seminal plasma antioxidant capacity. *J. Urol.* **161**, 1831–1834 (1999).
126. Mitropoulos, D. *et al.* Nitric oxide synthase and xanthine oxidase activities in the spermatic vein of patients with varicocele: a potential role for nitric oxide and peroxynitrite in sperm dysfunction. *J. Urol.* **156**, 1952–1958 (1996).
127. Romeo, C. *et al.* Preliminary report on nitric oxide-mediated oxidative damage in adolescent varicocele. *Hum. Reprod.* **18**, 26–29 (2003).
128. Smith, R. *et al.* Increased sperm DNA damage in patients with varicocele: relationship with seminal oxidative stress. *Hum. Reprod.* **21**, 986–993 (2006).
129. Barbieri, E. R., Hidalgo, M. E., Venegas, A., Smith, R. & Lissi, E. A. Varicocele-associated decrease in antioxidant defenses. *J. Androl.* **20**, 713–717 (1999).
130. Chen, S. S., Chang, L. S. & Wei, Y. H. Oxidative damage to proteins and decrease of antioxidant capacity in patients with varicocele. *Free Radic. Biol. Med.* **30**, 1328–1334 (2001).
131. Benoff, S. & Gilbert, B. R. Varicocele and male infertility: part, I. Preface. *Hum. Reprod. Update* **7**, 47–54 (2001).
132. Shiraishi, K. & Naito, K. Involvement of vascular endothelial growth factor on spermatogenesis in testis with varicocele. *Fertil. Steril.* **90**, 1313–1316 (2008).
133. Korff, T. & Augustin, H. G. Tensional forces in fibrillar extracellular matrices control directional capillary sprouting. *J. Cell Sci.* **112**, 3249–3258 (1999).
134. Ai, Q. Y. *et al.* Expressions of VEGF and Flt-1 in the testis, epididymis and epididymal sperm of adolescent rats [Chinese]. *Zhonghua Nan Ke Xue.* **14**, 871–875 (2008).
135. Zenke, U. & Turek, P. in *Office Andrology* (eds Patton, P. E. & Battaglia, D. E.) 155–168 (Humana Press, Totowa, 2005).
136. Romeo, C. *et al.* Nitric oxide production is increased in the spermatic veins of adolescents with left idiophatic varicocele. *J. Pediatr. Surg.* **36**, 389–393 (2001).
137. Mostafa, T. *et al.* Reactive oxygen species and antioxidants relationship in the internal spermatic vein blood of infertile men with varicocele. *Asian J. Androl.* **8**, 451–454 (2006).
138. Diamond, D. A. *et al.* Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. *J. Urol.* **178**, 1584–1588 (2007).
139. Baazeem, A. *et al.* Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur. Urol.* **60**, 796–808 (2011).
140. Evers, J. L. & Collins, J. A. Surgery or embolisation for varicocele in subfertile men. *Cochrane Database Syst. Rev.* **3**, CD000479 (2004).
141. Evers, J. L., Collins, J. A. & Vandekerckhove, P. Surgery or embolisation for varicocele in subfertile men. *Cochrane Database Syst. Rev.* **1**, CD000479 (2001).
142. Marmar, J. L. *et al.* Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis. *Fertil. Steril.* **88**, 639–648 (2007).
143. Rubenstein, R. A., Dogra, V. S., Seftel, A. D. & Resnick, M. I. Benign intrascrotal lesions. *J. Urol.* **171**, 1765–1772 (2004).
144. Baskin, L. S. & Kogan, B. A. in *Pediatric Urology Practice* (eds Gonzales, E. T. & Bauer, S. B.) 649–653 (Lippincott, Williams & Wilkins, Philadelphia, 1999).
145. Lipshultz, L. I., Thomas, A. J. & Khera, M. in *Campbell–Walsh Urology* 9th edn (eds Wein, A. J., Kavoussi, L. R., Novick, A. C., Partin, A. W. & Peters, C. A.) 577–608 (Elsevier, New York, 2007).
146. Esposito, C. *et al.* Incidence and management of hydrocele following varicocele surgery in children. *J. Urol.* **171**, 1271–1273 (2004).
147. Al-Kandari, A. M., Shabaan, H., Ibrahim, H. M., Elshebiny, Y. H. & Shokeir, A. A. Comparison of outcomes of different varicocelectomy techniques: open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy: a randomized clinical trial. *Urology* **69**, 417–420 (2007).
148. Mihmanli, I. *et al.* Testicular size and vascular resistance before and after hydrocelectomy. *AJR Am. J. Roentgenol.* **183**, 1379–1385 (2004).
149. Heyns, C. F. The gubernaculum during testicular descent in the human fetus. *J. Anat.* **153**, 93–112 (1987).
150. Skoog, S. J. Benign and malignant pediatric scrotal masses. *Pediatr. Clin. North Am.* **44**, 1229–1250 (1997).
151. Barthold, J. S. & Kass, E. J. in *Clinical Pediatric Urology* 4th edn (eds Belman, A. B., King, L. R. & Kramer, S. A.) 1093–1124 (Martin Dunitz, London, 2002).
152. Rowe, M. I., Copelson, L. W. & Clatworthy, H. W. The patent processus vaginalis and the inguinal hernia. *J. Pediatr. Surg.* **4**, 102–107 (1969).
153. Bronsther, B., Abrams, M. W. & Elboim, C. Inguinal hernias in children—a study of 1,000 cases and a review of the literature. *J. Am. Med. Womens Assoc.* **27**, 522–525 (1972).
154. Schneck, F. X. & Bellinger, M. F. in *Campbell–Walsh Urology* 9th edn (eds Wein, A. J., Kavoussi, L. R., Novick, A. C., Partin, A. W. & Peters, C. A.) 3761–3798 (Elsevier, New York, 2007).
155. Pierik, F. H., Dohle, G. R., van Muiswinkel, J. M., Vreeburg, J. T. & Weber, R. F. Is routine scrotal ultrasound advantageous in infertile men? *J. Urol.* **162**, 1618–1620 (1999).
156. Barthold, J. S. & Kass, E. J. in *Clinical Pediatric Urology* 4th edn (eds Belman, A. B., King, L. R. & Kramer, S. A.) 1093–1124 (Martin Dunitz, London, 2002).
157. Small, C. M. *et al.* Maternal exposure to a brominated flame retardant and genitourinary conditions in male offspring. *Environ. Health Perspect.* **117**, 1175–1179 (2009).
158. Kogan, S. J., Hadzieselmovic, F. & Howards, S. S. in *Adult and Pediatric Urology* 4th edn (eds Gillenwater, J. Y., Grayhack, J. T., Howards, S. S. & Mitchell, M. E.) 2570–2581 (Lippincott, Williams & Wilkins, Philadelphia, 2002).
159. Qublan, H. S., Al-Okoor, K., Al-Ghoweri, A. S. & Abu-Qamar, A. Sonographic spectrum of scrotal abnormalities in infertile men. *J. Clin. Ultrasound* **35**, 437–441 (2007).
160. Dandapat, M. C., Padhi, N. C. & Patra, A. P. Effect of hydrocele on testis and spermatogenesis. *Br. J. Surg.* **77**, 1293–1294 (1990).
161. Palep, H. S. Semen analysis parameters and effect of treatment with Asparagus Racemsus and Mucuna Pruriens. *Bombay Hosp. J.* **47**, 232–236 (2005).
162. Turgut, A. T. *et al.* Unilateral idiopathic hydrocele has a substantial effect on the ipsilateral testicular geometry and resistivity indices. *J. Ultrasound Med.* **25**, 837–843 (2006).
163. Bhatnagar, B. N., Dube, B. & Shukla, A. P. Testicular histology in tropical vaginal hydrocele. *Int. Surg.* **53**, 167–170 (1970).
164. Singh, M. P., Goel, T. C., Agarwal, P. K. & Singh, M. Effects of scrotal hydrocele over testicular histology. *Indian J. Pathol. Microbiol.* **32**, 261–265 (1989).
165. Mangoud, A. M. *et al.* Hydrocele in filarial and non filarial patients. Histopathological, histochemical and ultrastructural studies. *J. Egypt Soc. Parasitol.* **23**, 43–54 (1993).
166. Rados, N., Trnski, D., Keros, P. & Rados, J. The biomechanical aspect of testis hydrocele. *Acta Med. Croatica* **50**, 33–36 (1996).
167. Nye, P. J. & Prati, R. C. Jr. Idiopathic hydrocele and absent testicular diastolic flow. *J. Clin. Ultrasound* **25**, 43–46 (1997).
168. Zahalsky, M. P., Berman, A. J. & Nagler, H. M. Evaluating the risk of epididymal injury during hydrocelectomy and spermatocelectomy. *J. Urol.* **171**, 2291–2292 (2004).
169. Leung, M. L., Gooding, G. A. & Williams, R. D. High-resolution sonography of scrotal contents in asymptomatic subjects. *AJR Am. J. Roentgenol.* **143**, 161–164 (1984).
170. Dogra, V. S., Gottlieb, R. H., Oka, M. & Rubens, D. J. Sonography of the scrotum. *Radiology* **227**, 18–36 (2003).
171. Munden, M. M. & Trautwein, L. M. Scrotal pathology in pediatrics with sonographic imaging. *Curr. Probl. Diagn. Radiol.* **29**, 185–205 (2000).
172. Wollin, M., Marshall, F. F., Fink, M. P., Malhotra, R. & Diamond, D. A. Aberrant epididymal tissue: a significant clinical entity. *J. Urol.* **138**, 1247–1250 (1987).
173. Baskin, L. S., Himes, K. & Colborn, T. Hypospadias and endocrine disruption: is there a connection? *Environ. Health Perspect.* **109**, 1175–1183 (2001).
174. Paulozzi, L. J. International trends in rates of hypospadias and cryptorchidism. *Environ. Health Perspect.* **107**, 297–302 (1999).
175. Jarvis, L. J. & Dubbins, P. A. Changes in the epididymis after vasectomy: sonographic findings. *AJR Am. J. Roentgenol.* **152**, 531–534 (1989).
176. Takihara, H. The treatment of obstructive azoospermia in male infertility—past, present, and future. *Urology* **51** (5A Suppl.), 150–155 (1998).
177. Chiari, R. & Drujan, B. Dissection of spermatoceles and fertility (author's transl) [German]. *Urologe A* **19**, 68–271 (1980).
178. Kauffman, E. C., Kim, H. H., Tanrikut, C. & Goldstein, M. Microsurgical spermatocelectomy: technique and outcomes of a novel surgical approach. *J. Urol.* **185**, 238–242 (2011).
179. Beiko, D. T. & Morales, A. Percutaneous aspiration and sclerotherapy for treatment of spermatoceles. *J. Urol.* **166**, 137–139 (2001).
180. Pabst, R. Studies on structure and function of human ductus deferens [German]. *Z. Anat. Entwicklungsgesch.* **129**, 154–176 (1969).
181. Mulhall, J. P. & Oates, R. D. Vasal aplasia and cystic fibrosis. *Curr. Opin. Urol.* **5**, 316–319 (1995).
182. Donohue, R. E. & Fauver, H. Unilateral absence of the vas deferens—a useful clinical sign. *JAMA* **261**, 1180–1182 (1989).
183. Popli, K. & Stewart, J. Infertility and its management in men with cystic fibrosis: review of literature and clinical practices in the UK. *Hum. Fertil. (Camb.)* **10**, 217–221 (2007).
184. Taulan, M. *et al.* Large genomic rearrangements in the CFTR gene contribute to CBAVD. *BMC Med. Genet.* **8**, 22 (2007).

185. Ratbi, I. *et al.* Detection of cystic fibrosis transmembrane conductance regulator (CFTR) gene rearrangements enriches the mutation spectrum in congenital bilateral absence of the vas deferens and impacts on genetic counselling. *Hum. Reprod.* **22**, 1285–1291 (2007).
186. Anguiano, A. *et al.* Congenital bilateral absence of the vas deferens. A primarily genital form of cystic fibrosis. *JAMA* **267**, 1794–1797 (1992).
187. Donat, R., McNeill, A. S., Fitzpatrick, D. R. & Hargreave, T. B. The incidence of cystic fibrosis gene mutations in patients with congenital bilateral absence of the vas deferens in Scotland. *Br. J. Urol.* **79**, 74–77 (1997).
188. Shin, D., Gilbert, F., Goldstein, M. & Schlegel, P. N. Congenital absence of the vas deferens: incomplete penetrance of cystic fibrosis gene mutations. *J. Urol.* **158**, 1794–1798 (1997).
189. Jequier, A. M., Ansell, I. D. & Bullimore, N. J. Congenital absence of the vasa deferentia presenting with infertility. *J. Androl.* **6**, 15–19 (1985).
190. Goldstein, M. & Schlossberg, S. Men with congenital absence of the vas deferens often have seminal vesicles. *J. Urol.* **140**, 85–86 (1988).
191. Futterer, J. J., Heijmink, S. W. & Spermon, J. R. Imaging the male reproductive tract: current trends and future directions. *Radiol. Clin. North Am.* **46**, 133–147 (2008).
192. Patrizio, P. & Leonard, D. in *The Genetic Basis of Male Infertility Results and Problems in Cell Differentiation* (ed. McElreavey, K.) 175–186 (Springer–Verlag, Berlin, 2000).
193. Oates, R. D. & Amos, J. A. Congenital bilateral absence of the vas deferens and cystic fibrosis. A genetic commonality. *World J. Urol.* **11**, 82–88 (1993).
194. Silber, S. J., Patrizio, P. & Asch, R. H. Quantitative evaluation of spermatogenesis by testicular histology in men with congenital absence of the vas deferens undergoing epididymal sperm aspiration. *Hum. Reprod.* **5**, 89–93 (1990).
195. Hermann, B. M. in *Andrology: Male Reproductive Health and Dysfunction* 3rd edn (eds Nieschlag, E. & Nieschlag, S.) 263–278 (Springer, Berlin, 2010).
196. Silber, S. J. *et al.* The use of epididymal and testicular spermatozoa for intracytoplasmic sperm injection: the genetic implications for male infertility. *Hum. Reprod.* **10**, 2031–2043 (1995).
197. Jarrow, J. *et al*. The Evaluation of the Azoospermic Male: Best Practice Statement. *American Urological Association* [online], http://www.auanet.org/content/media/azoospermicmale2010.pdf (2010).
198. Klapproth, H. J. & Young, I. S. Vasectomy, vas ligation and vas occlusion. *Urology* **1**, 292–300 (1973).
199. Schmidt, S. S. Technics and complications of elective vasectomy. The role of spermatic granuloma in spontaneous recanalization. *Fertil. Steril.* **17**, 467–482 (1966).
200. Hall, S. & Oates, R. D. Unilateral absence of the scrotal vas deferens associated with contralateral mesonephric duct anomalies resulting in infertility: laboratory, physical and radiographic findings, and therapeutic alternatives. *J. Urol.* **150**, 1161–1164 (1993).
201. Engin, G., Kadioglu, A., Orhan, I., Akdol, S. & Rozanes, I. Transrectal US and endorectal MR imaging in partial and complete obstruction of the seminal duct system. A comparative study. *Acta Radiol.* **41**, 288–295 (2000).
202. Purohit, R. S., Wu, D. S., Shinohara, K. & Turek, P. J. A prospective comparison of 3 diagnostic methods to evaluate ejaculatory duct obstruction. *J. Urol.* **171**, 232–235 (2004).
203. Goluboff, E. T., Stifelman, M. D. & Fisch, H. Ejaculatory duct obstruction in the infertile male. *Urology* **45**, 925–931 (1995).
204. McIntyre, M. & Fisch, H. Ejaculatory duct dysfunction and lower urinary tract symptoms: chronic prostatitis. *Curr. Urol. Rep.* **11**, 271–275 (2010).
205. Philip, J., Manikandan, R., Lamb, G. H. & Desmond, A. D. Ejaculatory-duct calculus causing secondary obstruction and infertility. *Fertil. Steril.* **88**, e9–e11 (2007).
206. Paick, J. S. Transurethral resection of the ejaculatory duct. *Int. J. Urol.* **7** (Suppl.), S42–S47 (2000).
207. Sabanegh, E. A. A. in *Campbell–Walsh Urology* 9th edn (eds Wein, A. J., Kavoussi, L. R., Novick, A. C., Partin, A. W. & Peters, C. A.) 673 (Elsevier, New York, 2007).
208. Dik, P., Lock, T. M., Schrier, B. P., Zeijlemaker, B. Y. & Boon, T. A. Transurethral marsupialization of a medial prostatic cyst in patients with prostatitis-like symptoms. *J. Urol.* **155**, 1301–1304 (1996).
209. Hamper, U. M., Epstein, J. I., Sheth, S., Walsh, P. C. & Sanders, R. C. Cystic lesions of the prostate gland. A sonographic–pathologic correlation. *J. Ultrasound Med.* **9**, 395–402 (1990).
210. McDermott, V. G., Meakem, T. J. 3rd, Stolpen, A. H. & Schnall, M. D. Prostatic and periprostatic cysts: findings on MR imaging. *AJR Am. J. Roentgenol.* **164**, 123–127 (1995).
211. Galosi, A. B. *et al.* Cystic lesions of the prostate gland: an ultrasound classification with pathological correlation. *J. Urol.* **181**, 647–657 (2009).
212. Mayersak, J. S. Urogenital sinus-ejaculatory duct cyst: a case report with a proposed clinical classification and review of the literature. *J. Urol.* **142**, 1330–1332 (1989).
213. Kato, H., Komiyama, I., Maejima, T. & Nishizawa, O. Histopathological study of the mullerian duct remnant: clarification of disease categories and terminology. *J. Urol.* **167**, 133–136 (2002).
214. Li, S., Wang, X., Ye, H., Gao, W., Pu, X. & Yang, Z. Distribution profiles of transient receptor potential melastatin- and vanilloid-related channels in rat spermatogenic cells and sperm. *Mol. Biol. Rep.* **37**, 1287–1293 (2010).
215. Nghiem, H. T., Kellman, G. M., Sandberg, S. A. & Craig, B. M. Cystic lesions of the prostate. *Radiographics* **10**, 635–650 (1990).
216. Shabsigh, R., Lerner, S., Fishman, I. J. & Kadmon, D. The role of transrectal ultrasonography in the diagnosis and management of prostatic and seminal vesicle cysts. *J. Urol.* **141**, 1206–1209 (1989).
217. Kato, H. *et al*. Anatomical and histological studies of so-called Mullerian duct cyst. *Int. J. Urol.* **12**, 465–468 (2005).
218. Hinman, F. in *Atlas of Uro-Surgical Anatomy* (ed. Hinman, F.) 345–388 (WB Saunders, Philadelphia, 1993).
219. Ardill, R. H., Manivel, J. C., Beier-Hanratty, S., Ercole, C. & Letourneau, J. G. Epididymitis associated with mullerian duct cyst and calculus: sonographic diagnosis. *AJR Am. J. Roentgenol.* **155**, 91–92 (1990).
220. Littrup, P. J. *et al.* Transrectal US of the seminal vesicles and ejaculatory ducts: clinical correlation. *Radiology* **168**, 625–628 (1988).
221. Cho, I. R. *et al.* Magnetic resonance imaging in hemospermia. *J. Urol.* **157**, 258–262 (1997).
222. Thurnher, S., Hricak, H. & Tanagho, E. A. Mullerian duct cyst: diagnosis with MR imaging. *Radiology* **168**, 25–28 (1988).
223. Moukaddam, H. A., Haddad, M. C., El-Sayyed, K. & Wazzan, W. Diagnosis and treatment of midline prostatic cysts. *Clin. Imaging* **27**, 44–46 (2003).
224. Iglesias, C. G. *et al.* Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935–1980 *Am. J. Kidney Dis.* **2**, 630–639 (1983).
225. Davies, F. *et al.* Polycystic kidney disease re-evaluated: a population-based study. *Q. J. Med.* **79**, 477–485 (1991).
226. US Renal Data System. *USRDS annual data report* [online], http://www.usrds.org/atlas07.aspx (2007).
227. Harris, P. C. & Torres, V. E. Polycystic Kidney Disease, Autosomal Dominant. *GeneReviews* [online], http://www.ncbi.nlm.nih.gov/books/NBK1246 (2002).
228. Dalgaard, O. Z. Bilateral polycystic disease of the kidneys; a follow-up of two hundred and eighty-four patients and their families. *Acta Med. Scand.* **328** (Suppl.), 1–255 (1957).
229. Danaci, M. *et al.* The prevalence of seminal vesicle cysts in autosomal dominant polycystic kidney disease. *Nephrol. Dial. Transplant.* **13**, 2825–2828 (1998).
230. Torra, R. *et al.* Prevalence of cysts in seminal tract and abnormal semen parameters in patients with autosomal dominant polycystic kidney disease. *Clin. J. Am. Soc. Nephrol.* **3**, 790–793 (2008).
231. Fang, S. & Baker, H. W. Male infertility and adult polycystic kidney disease are associated with necrospermia. *Fertil. Steril.* **79**, 643–644 (2003).
232. Hendry, W. F., Rickards, D., Pryor, J. P. & Baker, L. R. Seminal megavesicles with adult polycystic kidney disease. *Hum. Reprod.* **13**, 1567–1569 (1998).
233. Manno, M. *et al.* Polycystic kidney disease and infertility: case report and literature review. *Arch. Ital. Urol. Androl.* **77**, 25–28 (2005).
234. Handelsman, D. J. & Dong, Q. Hypothalamo-pituitary gonadal axis in chronic renal failure. *Endocrinol. Metab. Clin. North Am.* **22**, 145–161 (1993).
235. Pazour, G. J., Agrin, N., Leszyk, J. & Witman, G. B. Proteomic analysis of a eukaryotic cilium. *J. Cell Biol.* **170**, 103–113 (2005).
236. Pazour, G. J. & Witman, G. B. The vertebrate primary cilium is a sensory organelle. *Curr. Opin. Cell Biol.* **15**, 105–110 (2003).
237. Jain, R. *et al.* Temporal relationship between primary and motile ciliogenesis in airway epithelial cells. *Am. J. Respir. Cell. Mol. Biol.* **43**, 731–739 (2010).
238. Okada, H. *et al.* Assisted reproduction for infertile patients with 9 + 0 immotile spermatozoa associated with autosomal dominant polycystic kidney disease. *Hum. Reprod.* **14**, 110–113 (1999).
239. Vora, N., Perrone, R. & Bianchi, D. W. Reproductive issues for adults with autosomal dominant polycystic kidney disease. *Am. J. Kidney Dis.* **51**, 307–318 (2008).
240. Gao, Z., Ruden, D. M. & Lu, X. PKD2 cation channel is required for directional sperm movement and male fertility. *Curr. Biol.* **13**, 2175–2178 (2003).
241. Neill, A. T., Moy, G. W. & Vacquier, V. D. Polycystin-2 associates with the polycystin-1 homolog, suREJ3, and localizes to the acrosomal region of sea urchin spermatozoa. *Mol. Reprod. Dev.* **67**, 472–477 (2004).

242. Ridgway, P. F., Shah, J. & Darzi, A. W. Male genital tract injuries after contemporary inguinal hernia repair. *BJU Int.* **90**, 272–276 (2002).
243. Junge, K. *et al.* Influence of mesh materials on the integrity of the vas deferens following Lichtenstein hernioplasty: an experimental model. *Hernia* **12**, 621–626 (2008).
244. Cam, C., Celik, C., Sancak, A., Iskender, C. & Karateke, A. Inguinal herniorrhaphy in childhood may result in tubal damage and future infertility. *Arch. Gynecol. Obstet.* **279**, 175–176 (2009).
245. Ribarski, I. *et al.* USP26 gene variations in fertile and infertile men. *Hum. Reprod.* **24**, 477–484 (2009).
246. Kukuvitis, A. *et al.* Congenital obstructive azoospermia in a man with Marfan syndrome. *Fertil. Steril.* **76**, 1256–1257 (2001).
247. Dekker, H. M., de Jong, I. J., Sanders, J. & Wolf, R. F. Persistent Mullerian duct syndrome. *Radiographics* **23**, 309–313 (2003).
248. Tackett, L. D. *et al.* Incidence of contralateral inguinal hernia: a prospective analysis. *J. Pediatr. Surg.* **34**, 684–687 (1999).
249. Hawn, M. T. *et al.* Patient-reported outcomes after inguinal herniorrhaphy. *Surgery* **140**, 198–205 (2006).
250. Suominen, J. J. Sympathetic auto-immune orchitis. *Andrologia* **27**, 213–216 (1995).
251. Kemmotsu, H., Oshima, Y., Joe, K. & Mouri, T. The features of contralateral manifestations after the repair of unilateral inguinal hernia. *J. Pediatr. Surg.* **33**, 1099–1102 (1998).
252. Marulaiah, M., Atkinson, J., Kukkady, A., Brown, S. & Samarakkody, U. Is contralateral exploration necessary in preterm infants with unilateral inguinal hernia? *J. Pediatr. Surg.* **41**, 2004–2007 (2006).
253. Matsuda, T. *et al.* Seminal tract obstruction caused by childhood inguinal herniorrhaphy: results of microsurgical reanastomosis. *J. Urol.* **159**, 837–840 (1998).
254. Kusnierczyk, R., Piatkowski, W. & Wojcik, A. Inguinal hernia repair with the peduncled fascial flap: a new surgical technique. *Hernia* **13**, 161–166 (2009).
255. Awad, S. S. *et al.* Improved outcomes with the Prolene Hernia System mesh compared with the time-honored Lichtenstein onlay mesh repair for inguinal hernia repair. *Am. J. Surg.* **193**, 697–701 (2007).
256. Awad, S. S., Bruckner, B. & Fagan, S. P. Transperitoneal view of the PROLENE hernia system open mesh repair. *Int. Surg.* **90** (3 Suppl.), S63–S66 (2005).
257. Pollak, R. & Nyhus, L. M. Complications of groin hernia repair. *Surg. Clin. North Am.* **63**, 1363–1371 (1983).
258. Matsuda, T., Muguruma, K., Horii, Y., Ogura, K. & Yoshida, O. Serum antisperm antibodies in men with vas deferens obstruction caused by childhood inguinal herniorrhaphy. *Fertil. Steril.* **59**, 1095–1097 (1993).
259. Gomez-Perez, R., Osuna, J. A. & Arata-Bellabarba, G. Surgical vs. untreated cryptorchidism: effects on fertility. *Arch. Androl.* **50**, 19–22 (2004).
260. Okuyama, A. *et al.* Surgical management of undescended testis: retrospective study of potential fertility in 274 cases. *J. Urol.* **142**, 749–751 (1989).
261. Albescu, J. Z., Bergada, C. & Cullen, M. Male fertility in patients treated for cryptorchidism before puberty. *Fertil. Steril.* **22**, 829–833 (1971).
262. Mandat, K. M., Wieczorkiewicz, B., Gubala-Kacala, M., Sypniewski, J. & Bujok, G. Semen analysis of patients who had orchidopexy in childhood. *Eur. J. Pediatr. Surg.* **4**, 94–97 (1994).
263. Gilhooly, P. E., Meyers, F. & Lattimer, J. K. Fertility prospects for children with cryptorchidism. *Am. J. Dis. Child.* **138**, 940–943 (1984).
264. Lee, P. A., Coughlin, M. T. & Bellinger, M. F. Paternity and hormone levels after unilateral cryptorchidism: association with pretreatment testicular location. *J. Urol.* **164**, 1697–1701 (2000).
265. Coughlin, M. T. *et al.* Time to conception after orchidopexy: evidence for subfertility? *Fertil. Steril.* **67**, 742–746 (1997).
266. Hadziselimovic, F., Hadziselimovic, N. O., Demougin, P. & Oakeley, E. J. Testicular gene expression in cryptorchid boys at risk of azoospermia. *Sex Dev.* **5**, 49–59 (2011).
267. Hansen, T. S. Fertility in operatively treated and untreated cryptorchidism. *Proc. R. Soc. Med.* **42**, 645–651 (1949).
268. Shafik, A., El-Sibai, O. & Shafik, I. Electro-orchidogram: a non-invasive diagnostic tool in testicular pathologies. *Med. Sci. Monit.* **12**, MT51–MT55 (2006).

Author contributions

R. Singh, A. Hamada and L. Bukavina researched data for the article. R. Singh, A. Hamada and A. Agarwal contributed to the discussion of content. A. Hamada, L. Bukavina and A. Agarwal wrote the article. A. Hamada and A. Agarwal reviewed the manuscript before submission.

Online correspondence

Nature Reviews Urology publishes items of correspondence online only. Such contributions are published at the discretion of the Editors and can be subject to peer review. Correspondence should be no longer than 500 words with up to 15 references and up to two display items, and should represent a scholarly attempt to comment on a specific article that has been published in this journal. To view the correspondence published with this issue, please go to our homepage at http://www.nature.com/nrurol and follow the link from the current table of contents.

The following letters have recently been published:

What can academia learn from XMRV studies?
Chungen Pan, Xiaochu Ma and Shibo Jiang
doi:10.1038/nrurol.2011.225-c1

The author's reply:
Learning from a controversy
Karen Sfanos, Amanda Aloia, Angelo De Marzo and Alan Rein
doi:10.1038/nrurol.2011.225-c2