Cryptorchidism: classification, prevalence and long-term consequences

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Abstract

Undescended testis is a common finding in boys, and the majority of cases have no discernible aetiology. There are unexplained geographical differences and temporal trends in its prevalence. Cryptorchidism, especially bilateral, is associated with impaired spermatogenesis and endocrine function and increases the risk of testicular cancer. There is an urgent need to identify factors that adversely affect testicular development and optimize treatment.

Conclusion: Cryptorchidism may reflect a primary testicular maldevelopment with long-term consequences.

INTRODUCTION

Cryptorchidism or undescended testes is a very frequent clinical finding in boys. The regulation of prenatal testicular descent in humans is not fully understood, but numerous genetic and endocrine factors are involved (1,2).

The optimal treatment regimen for cryptorchidism remains unknown (3,4), and there is no systematic follow-up of patients into adulthood. Cryptorchidism may have long-term consequences on testicular function, including spermatogenesis, and on the risk for testicular cancer, even after successful treatment. Cryptorchidism has been proposed to be part of a ‘testicular dysgenesis syndrome’, which also includes hypospadias, reduced semen quality, and testicular cancer. These conditions are thought to have a common origin in prenatal testicular maldevelopment, which affects both Leydig and Sertoli cells and germ cell differentiation (5). There is emerging evidence that such testicular dysgenesis may be caused by environmental factors (6).

This review summarizes current knowledge about the prevalence of cryptorchidism and its development over time, the association of cryptorchidism with endocrine or genetic disorders and morphological developmental abnormalities, and its consequence for male reproductive health.

CLASSIFICATION OF CRYPTORCHIDISM

Terms such as undescended testis, retentio testis, cryptorchidism, and maldescensus testis describe a testis that is not normally located at the bottom of the scrotum. An undescended testis may be situated along its normal route of descent or in an ectopic position. In the clinical setting, a differentiation between palpable and non-palpable and uni or bilaterally undescended testes appears to be the most practical in determination of whom to treat (3).

However, for future studies on the aetiology and epidemiology of undescended testes and in order to improve the comparability of treatment studies, it would be advisable to apply a more differentiated classification system. Preferably, such a system should describe the precise testicular position (high/low abdominal, inguinal, supra scrotal, high scrotal and ectopic), its position over time during infancy and childhood (spontaneous descent, spontaneous ascent), as well as any known aetiological factors such as previous inguinal surgery (iatrogenic cryptorchidism). Few investigators use a distance between the top of the pubic crest and the middle of the testes of <4 cm in mature boys (<2.5 cm in prematurity) as an indication of undescended testis (7). The retractile testis represents a normal variant of testicular position. Such a testis is not initially found in the lower part of the scrotum, but can be manipulated without pain into a low scrotal position and remains there (8).

EXAMINATION

The diagnosis of undescended testis is not always easy to establish and depends to a large extent on the experience of the investigator and the examination set up. Clinical examination in warm surroundings includes a visual description of the scrotum and an examination of the child while supine, in crossed-leg position and, if possible, in upright standing position. Asymmetric and hypoplastic scrotum suggests unilateral or bilateral cryptorchidism, respectively. A unilateral non-palpable testis and an enlarged contralateral testis,
especially after the onset of puberty, may suggest testicular absence or atrophy. However, this finding is not specific and does not exclude the need for surgical exploration. The examiner should inhibit the cremasteric reflex with his nondominant hand above the pubic bone in the groin region before touching, or reaching, for the scrotum. The groin region may be ‘milked’ towards the scrotum in an attempt to move a cryptorchid testis into the scrotum. This manoeuvre also allows the differentiation between an inguinal testis and enlarged lymph node (9). Visual attention should be given to the femoral, penile and perineal region in case of a non-palpable testis to exclude an ectopic testis. Any undescended testis after the age of 6 months should be referred for orchiopexy (10).

PREVALENCE OF CRYPTORCHIDISM AND RISK FACTORS

The reported prevalence of cryptorchidism from prospective investigations of term and/or normal weight boys at birth varies between 2% and 8% (Table S1), indicating yet unexplained geographic differences. Congenital cryptorchidism may resolve spontaneously, and this descent occurs mostly during the first months of life, when the endogenous testosterone secretion briefly increases. Thus, a lower prevalence of 1–2% is reported from 3 to 12 months of life. These data are not directly comparable to results of registry or orchiopexy studies (11). In two school surveys of prepubertal boys prevalence rates up to 7% were reported (12,13). This increase during childhood is most likely due to acquired cryptorchidism, i.e. ascensus testis and severely retractile testes.

A birth weight <2.5 kg, being small for gestational age and prematurity are considerably risk factors of cryptorchidism (Table S1). Placental insufficiency with decreased HCG secretion may be one underlying factor (14), as well as low maternal estrogen levels (15). Intra-uterine growth plays a key role for many male reproductive disorders (16,17).

There is emerging evidence that environmental factors may also play a role for the risk of cryptorchidism in humans (6). Exposure to environmental chemicals, i.e. persistent organochlorines, phthalate monoesters and smoking, has recently been linked to adverse effects in infant reproductive development (18–21). Maternal diabetes, including gestational diabetes, also appears to be a risk factor for cryptorchidism (22,23).

In conclusion, the reported prevalence of cryptorchidism depends on examination skills, classification systems, selection of study populations and the child’s age at examination. Prospective cohort studies indicate a yet unexplained geographic difference in the prevalence of congenital cryptorchidism.

TRENDS IN THE PREVALENCE OF CRYPTORCHIDISM

Prospective standardized cohort studies have indicated an increase in the prevalence of congenital cryptorchidism in England between the 1950s and 1980s and in Denmark between the 1960s and 2000 (Table S1). This time trend is in line with the increasing prevalence of hypospadias, reduced semen quality and testicular cancer in some Western countries (24,25) and suggests that changes in lifestyle and environment are likely to play a role.

Data based on the ICBDMS (International Clearinghouse for Birth Defects Monitoring Systems) suggested that the rate of cryptorchidism had increased in the US, Canada and South America in the 1970s and 1980s. However, in most registries the rates declined after 1985 (25). In general, the validity of registry data may, however, be compromised by underreporting and variation in diagnostic criteria.

Orchidopexy rates in England and Wales doubled between 1952 and 1977 (26), but two recent studies showed a 33% decrease between 1992 and 1998 in the UK (27) and a 17% decrease in Denmark from 1990 to 2000 (21). Orchidopexies rates include congenital and acquired forms of cryptorchidism as well as some retractile testes, and can therefore not be directly compared to population prevalences of congenital cryptorchidism.

CRYPTORCHIDISM AS PART OF AN UNDERLYING DISEASE

Cryptorchidism can occur as an isolated disorder in healthy boys, but it can also be part of endocrine or genetic disorders, syndromes and morphological abnormalities.

ENDOCRINE DISEASES AND DISORDERS OF SEXUAL DIFFERENTIATION

Normal testicular descent is dependent on an intact hypothalamus–pituitary–testicular axis. Malformations of the central nervous system, i.e. holoprosencephaly, and congenital hypogonadotropic hypogonadism may be associated with cryptorchidism (28). Gonadotropin deficiency with anosmia (Kallmann syndrome) can be caused by mutations of the anosmin-1 gene (KAL1, X-linked) (43) or inactivating mutations of the fibroblast growth factor-1 receptor gene (FGFR1, autosomal recessive). Genes involved in isolated hypogonadotropic hypogonadism include the GnRH receptor, GPR54 (receptor of the Kiss1-derived peptide receptor), DAX1 (associated with congenital adrenal hypoplasia) and two genes associated with obesity, leptin (OB) and leptin receptor (DB). Hypogonadotropic hypogonadism may be part of multiple pituitary insufficiency due to septooptic dysplasia (HESX1 mutation), Börjeson-Lehmann syndrome (PHF6 mutation) and PROP1 mutations (28,29).

Cryptorchidism with ambiguous genitalia always needs immediate systematic work-up (30). Insufficient androgen production or action will induce undervirilization of the 46,XY male, like deficiencies of the 5α-reductase, STAR protein, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase/17-20 lyase or 17β-hydroxysteroid dehydrogenase and androgen receptor mutations causing androgen resistance. In the complete forms of Leydig cell hypoplasia or androgen resistance, the external genitalia are female, with testes located intra-abdominally or in the groin. Incomplete forms may present with a wide phenotypic spectrum from isolated mild hypospadias to clitoral hypertrophy with a normal vagina positioning and no palpable testes. Persistent
Müllerian duct syndrome, caused by lack of synthesis or action of the anti-Müllerian hormone, shows no ambiguity of the male external genitalia, but the internal genitalia include fallopian tubes and a uterus and cryptorchidism is frequent.

In gonadal dysgenesis, the gonads have failed to fully differentiate and the appearance of the external genitalia can range from obviously female to obviously male. In its most common form, mixed gonadal dysgenesis, a dysgenetic testis is found together with a streak gonad. The karyotype may vary, but frequently a 45,X cell line can be found. Cryptorchidism and testicular dysgenesis or a development of streak gonads may also be seen in chromosome 9p deletion, campomelic dysplasia (SOX9 mutation) and mutations in the WT-1 or SRY genes (30).

In a phenotypically male newborn with bilateral nonpalpable testes, it is important to exclude a severely virilized genetic female, like in congenital adrenal hyperplasia, placental aromatase deficiency or maternal hyperandrogenism (30).

SYNDROMES AND COMPLEX MALFORMATIONS
Cryptorchidism is a component of many syndromes with multiple congenital anomalies, although the mechanisms for testicular maldescent in most conditions remain to be elucidated (Table S2). Cryptorchidism is also associated with the prune-belly syndrome, the bladder exstrophy complex, renal and urinary tract anomalies, hypospadias, imperforate anus, neural tube defects and other caudal developmental field defects (31,32). Intra-abdominal testes may be associated with an abnormal differentiation of the midline developmental field (11). As body components of one embryonic developmental field, i.e. the midline or the caudal part of the body, have to evolve in a coordinated fashion, any disruption of one organ system development may result in abnormalities of the others.

SEmen QUALITY AND CRYPTORCHIDISM
Most previous studies of semen quality in cryptorchidism have used the WHO criteria of 20 x 10^6/mL as lowest normal concentration (Table S3). Adult men with persistent bilateral cryptorchidism have azoospermia, whereas 28% (95% confidence intervals: 24–32%) after operation have a normal sperm count. Approximately 49% (41–58%) of men with persistent unilateral cryptorchidism have a normal sperm concentration as compared to 71% (68–74%) after orchidopexy. Reduced paternity rates have been found after treatment for bilateral (33), but not unilateral cryptorchidism (34,35).

Few studies have assessed semen quality in relation to age at orchidopexy. Due to different previous guidelines, the age range is usually higher than in current recommendations. Surgery between 10 months and 4 years of age in bilateral cryptorchidism led to a normal sperm count in 76% (50–93%), compared to 26% (9–51%) with surgery between 4 and 14 years. In unilateral cryptorchidism this impact of timing was not as obvious: 75% (68–81%) versus 71% (61–80%) if operated between 10 months and 6 years versus 9–12 years.

It is yet unknown, whether current guidelines of earlier orchiopexy would further improve this outcome.

REPRODUCTIVE HORMONES IN CRYPTORCHIDISM
Changes in testicular endocrine function due to cryptorchidism have been documented from early puberty to adulthood (33,36), whereas results in childhood are controversial (37–41). In 5-month-old cryptorchid boys inhibin B values were decreased and FSH increased (40) depending on the severity of the condition. Also high scrotal testes and cryptorchid testes with spontaneous post-natal descent showed a subtle impairment of the pituitary–gonadal axis (40). The long-term consequences of these findings are not yet known. In older cryptorchid boys, however, hereof 75% unilateral, inhibin B serum levels were within the normal range (39). Inhibin B was low in some boys with a low number of germ cells at biopsy (37,41) or impalpable testes (41). Increasing levels of inhibin B were reported in the majority of boys six months after successful surgery (41).

In adulthood, higher levels of inhibin B were found in men who underwent orchidopexy before two years of age than later (36). In infertile men, lower inhibin B and higher FSH levels were found if there was a history of cryptorchidism (42). Late orchidopexy appeared to also have an adverse effect on Leydig cell function (43,44).

Thus, inhibin B and FSH may be useful markers for Sertoli cell function before and after orchidopexy. However, the prediction of future fertility should be done with great care until data from long-term follow-up of patients are available.

CRYPTORCHIDISM AND TESTIS CANCER
Cryptorchidism is a well-established risk factor for testicular neoplasia, but the proportion of testicular cancer that is attributable to cryptorchidism is only approximately 5% (16). In a recent metaanalysis of 21 case-control studies of the epidemiology of germ cell tumours, increased odds ratios for having testicular cancer in patients with a history of cryptorchidism ranged from 3.5 to 17.1. The overall relative risk was 4.8 (4.0–5.7) (45).

The aetiology of testicular germ cell cancer remains unknown, but epidemiological studies have linked the majority of risk factors with intra-uterine and perinatal testicular development, and several of these factors have also been associated with cryptorchidism (5,45,46). Testicular germ cell cancer originates from a pre-invasive lesion, the carcinoma in situ testis (CIS) (47), known also as ‘intra-tubular germ cell neoplasia unclassified’. The pathogenesis of malignant transformation of germ cells into CIS cells has not yet been elucidated in detail. A currently prevalent model postulates that the initiation step is a developmental arrest of primordial germ cells or gonocytes, as these cell types exhibit common phenotypic features with CIS cells (48). The developmentally arrested cell then undergoes malignant transformation, which is probably associated with adaptive genomic and gene expression changes (48). Development of overt tumours usually takes place in young adults, as CIS cells begin to proliferate rapidly after the onset of puberty.
In a study of 300 men, previously admitted for orchiopexy, testicular biopsy in adulthood showed CIS in 1.7% (95% CI interval: 0.3–3.9%) and two men had been diagnosed with overt testicular cancer prior to the study (49). It was estimated that adult men with a history of cryptorchidism had a prevalence of CIS of approximately 2.9% (1.8–4.1) (50). In general, biopsy of undescended testis in childhood in order to examine for CIS cannot be recommended (11). One case of CIS was recently reported in a retractile testis, although a chance finding cannot be excluded (51). However, if cryptorchidism is combined with disorders of sexual differentiation or abnormal karyotype, i.e. in mixed gonadal dysgenesis, a biopsy is recommended at the time of surgery in childhood, as there is a substantially increased risk of neoplasia (11,52). A previous suspicion, that testicular biopsy itself may increase the risk of testicular cancer, could not be reproduced in a large cohort study (16).

Bilateral cryptorchidism carries a higher risk of malignancy than unilateral (16). In unilateral cryptorchidism most tumours occur in the affected testis, but in 8–15% of cases they occur in the contralateral scrotal testis (53). Although the risk for testicular cancer in the normally descended testis is thus much lower than in the unilaterally cryptorchid testis, the relative risk (estimated at 1.6–2.1) still slightly exceeds that of non-cryptorchid men (45). The risk of developing germ cell tumour is usually greater if the testis is located in intra-abdominally. In a recent study 40% of persistent impalpable testes in adult men had germ cell tumours (54). However, the lowest risk of cancer development is found in the complete form of androgen insensitivity, which often presents with intra-abdominal testes. Here, some undifferentiated germ cells with CIS-like features may persist for many years without progressing into an invasive tumour (55–58). To our knowledge, no cases of testicular cancer have been reported in patients with complete hypogonadotropic hypogonadism, who also may present with intra-abdominal testes.

In several studies, cryptorchidism operated before 8, 10 or 11 years of age or showing spontaneous descent, was not associated with an increased risk of testicular cancer (16,59,60). However, the majority of previous studies include patients operated after 2 years of age, when the potential transformation of poorly differentiated germ cells into CIS cells may already have taken place. Information about the success or orchiopexy (59) or the proportion of patients with untreated cryptorchidism at the time of cancer diagnosis is not reported (16,59). It therefore remains to be seen whether the currently recommended younger age at orchiopexy will lead to a decrease in testis cancer risk.

In summary, there is an association between cryptorchidism and testicular cancer, although only a small fraction of patients develop both disorders during lifetime.

CONCLUSIONS
Cryptorchidism is a common finding in boys, which requires expert assessment and treatment. For unknown reasons, the prevalence of cryptorchidism appears to have increased over the past decades in some countries. This is of concern, since cryptorchidism, even after treatment, is associated with long-term adverse health effects, such as impaired semen quality and an increased risk of testicular cancer. This is especially pertinent for bilateral cryptorchidism. Cryptorchidism can reflect an underlying endocrine or genetic disorder or an abnormal development of the midline or the caudal part of the body. In the majority of cases, however, it is impossible to establish a cause with certainty. The apparent increase in the prevalence of cryptorchidism in some areas and the geographic differences suggest that genetic and environmental factors play a role. Other male reproductive disorders, i.e. hypospadias, reduced semen quality and testicular cancer, show similarities in their geographical distribution and temporal trends as cryptorchidism. They also share common risk factors, which suggests a prenatal impairment of testicular development as a common cause of these disorders.

There remains a significant challenge for clinicians and researchers with respect to the aetiology and the possibility of prevention of cryptorchidism as well as optimal treatment regimens.

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Clinical aspects of cryptorchidism


Supplementary material

The following supplementary material is available for this article:

**Table S1** The prevalence of cryptorchidism in boys born at term and/or with a birth weight ≥ 2500 g and infant boys in cohort studies

**Table S2** Syndromes associated with cryptorchidism

**Table S3** Frequency of men with a sperm count ≥20×10⁶/mL grouped according to the severity of cryptorchidism (unilateral/bilateral) and treatment (persistent/post-surgery) (11)

References for Tables S1–S3.

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