Epidemiology, pathophysiology, and pathogenesis of cryptorchidism. Evaluation and treatment of undescended testicle

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ABSTRACT

Cryptorchidism – the absence of one or both testes in the normal scrotal position – is the most common birth defect of the male genitalia. In full-term newborn boys its incidence is estimated at 2–5%. During the first three months of life, in half of these boys the testicles will descend spontaneously into the scrotum, but at the end of the first year of life 1% of boys will have cryptorchidism. Among boys born prematurely, about 30% of them have undescended testicles at birth, but also in such cases approximately 80% of undescended testes descend by the third month of life. The authors discuss the epidemiology, pathophysiology, aetiology, and treatment of undescended testicle in boys.

KEY WORDS: cryptorchidism, undescended testicle, boys, epidemiology, pathophysiology, aetiology.

INTRODUCTION

Cryptorchidism – the absence of one or both testicles in the normal scrotal position is the most common birth defect of the male genitalia. In full-term newborn boys its incidence is estimated at 2–5% [1]. During the first three months of life, in half of these boys the testicles will descend spontaneously into the scrotum, but at the end of the first year of life 1% of boys will have cryptorchidism [2]. Among boys born prematurely, about 30% have undescended testicles at birth, but also in such cases approximately 80% of undescended testes descend by the third month of life [3]. Most cases of cryptorchidism are isolated without other innate malformations; few are constituents of genetic or endocrine syndromes [1]. Over the years some testicles become retractile. This problem usually resolves spontaneously before or during puberty, but in rare cases the retractile testicle remains in the groin and is no longer movable. Recurrent cryptorchidism is defined as cryptorchid testes that were undescended at birth, descended spontaneously, and are subsequently defined as extrascrotal [4]. Secondary cryptorchidism and testicular retraction have been used to describe testes that are suprascrotal after inguinal hernia repair and as a complication of orchidopexy, respectively [4]. Testicular malposition after hernia repair could be caused by either postoperative scarring or primary maldescent [4].

There is conflicting evidence as to the changes of occurrence of cryptorchidism. Over the last decades some authors have reported an increasing incidence of this pathology, while [2, 5, 6] others report stable or decreasing numbers of boys with undescended testicles [7–9].

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TESTICULAR DESCENT

Testicular descent is a two-phase process that starts at the eighth week of gestation and should be completed by the third trimester of pregnancy. During the first trans-abdominal phase, the testicle is guided to the lowest part of abdominal cavity by hypertrophy and growth of the gubernaculum. This phase is regulated by hormonal factors produced by the foetal testis, such as insulin-like 3 protein (INSL3) and androgens [4].

The second inguinoscrotal phase of the testicular descent depends on androgens that induce a cellular proliferation in the gubernaculum [4].

EVALUATION

The undescended testicle may be found along the "path of descent", such as: the retroperitoneal part of the abdomen, the internal inguinal ring, and inside the inguinal canal [10]. In rare cases an undescended testicle, takes a non-standard path and ends up in front of the thigh, femoral canal, skin of the penis, or behind the scrotum. These testis are referred to as ectopic [10].

Over 70% of undescended testicles are palpable during physical examination and do not need imaging evaluation [10]. In the remaining cases of non-palpable testes, the diagnostics should confirm the absence or presence of the testes and identify their location. The most commonly used imaging study evaluating undescended testicles is ultrasound, with the sensitivity and specificity to localise nonpalpable testes at 45% and 78%, respectively [11]. Computed tomography (CT) scanning should not be used routinely because of the radiation exposure and high costs [11]. Routine karyotype investigation of all patients with cryptorchidism does not seem necessary. In cases with ambiguous genitalia, a karyotype can confirm or exclude dysgenetic primary hypogonadism [1].

In 2014 the American Urologic Association (AUA) presented current guidelines for the evaluation and treatment of cryptorchidism [12].

PATHOPHYSIOLOGY

Descent of the testes into the lower temperature environment of the scrotum is crucial for future successful reproduction. Cryptorchidism is associated with decreased fertility, increased incidence of testicular germ cell tumours, and testicular torsion, and it can be a source of psychological problems [1–3].

Among men who develop testicular cancer, 5–9% have persistent cryptorchidism [2, 13–15]. Men with cryptorchidism operated on after puberty were 2–6-fold more likely to have had testicular cancer compared to men who received corrective treatment before the age of 12 years [16, 17]. Contrary to that observation, according to Khatwa et al., the risk of cancer remains the same independently of the age of orchidopexy [18].

Men born with cryptorchidism are twice as likely to have reduced fertility when compared to those born with their testes in the scrotum, even after orchidopexy [2, 18, 19]. The reduction of fertility in men operated on because of bilateral cryptorchidism is estimated at 38% (infertility and azoospermia) [20]. According to latest research, fertility rates of patients operated for unilateral cryptorchidism are comparable to those seen in normal males [20]. Degeneration of spermatogenic tissue and reduced spermatogonia counts were observed after just the second year of life in patients born with cryptorchidism [20]. Also, the results of a survey by Matuszczak et al. suggest that the rise of the levels of MMP-1 and MMP-2 in the plasma of boys with cryptorchidism may reflect the level of apoptosis of the germ cells in undescended testicles, in response to heat stress [21, 22]. Those results prompt the recommendation for early surgery.

CLASSIFICATION

Cryptorchidism may be unilateral or bilateral, with a predominance of the right side (70–80%) [1–3, 5–7]. The undescended testis may be found anywhere on its path from the abdomen to the scrotum, starting from the high retroperitoneal position, through the inguinal canal, external ring, prescrotal to upper scrotal, or in an ectopic position (usually in the superficial inguinal pouch or perineal). There are also cases of hypoplastic, dysgenetic, or missing testicles. Around 80% of undescended testicles are reachable during physical examination within the inguinal canal or high scrotal area, whereas 20% of undescended testicles are not palpated [1–3, 5–7].

Nowadays, diagnostic laparoscopy is the gold standard that can confirm the absence of testis in patients with nonpalpable unilateral and many bilateral cryptorchidism [8–10].

The most commonly used radiological test evaluating undescended testes is ultrasound, which has the sensitivity and specificity to localise nonpalpable testes at 45% and 78%, respectively [8–10]. CT scanning should not be used routinely because of the radiation exposure and high costs [8–10].

MRI stands out with great sensitivity and specificity, but its use is determined by high costs, low availability, and the need for anaesthesia [8–10].

TREATMENT

To reduce risks described above, undescended testes should be brought into the scrotum operatively by an orchidopexy, which is recommended between the ages of 6 and 18 months [2, 23, 24]. For boys born prematurely the timing of the operation should be determined using corrected age [20]. Ascending testes diagnosed in child-
hood should immediately be treated surgically [2, 25, 26]. The American Urological Association does not recommend hormonal therapy to induce testicular descent because evidence shows low response rates and lack of evidence for long-term efficacy [12]. In boys with undescended testes that are palpable, scrotal or inguinal orchiopexy should be performed. In boys with nonpalpable testes, examination under anaesthesia followed by surgical exploration and, if indicated, abdominal orchiopexy should be performed. During surgical exploration the testicular vessels should be identified. In the case of very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age and a normal contralateral testis, an orchiectomy should be performed. Parents should be counselled regarding potential long-term risks, infertility, and cancer [12].

AETIOLOGY

The aetiology of cryptorchidism is complex. Correct testicular descent depends on the hypothalamic-pituitary-gonadal axis. According to the literature, a combination of genetic, maternal, and environmental factors affect testicular development and descent.

Possible risk factors for cryptorchidism given in the literature include:
- prematurity,
- low birth weight,
- small for gestational age,
- maternal factors: age, obesity, diabetes, maternal alcohol consumption, maternal cigarette smoking,
- in vitro fertilisation,
- low parity,
- twinning,
- sex hormone imbalance,
- endocrine disrupting chemicals,
- family history, genetic alterations, and congenital genetic syndromes – Klinefelter syndrome, Down syndrome, Prader-Willi syndrome, Noonan syndrome.

Many authors agree that the incidence of cryptorchidism correlates positively with prematurity, low birth weight, and small size for gestational age [2, 27–30].

MATERNAL FACTORS

A positive correlation between older (> 30 years) and younger (< 20 years) age of mothers and cryptorchidism in sons was observed, but contrary to this observation Jones et al. and McGlynn et al. found that young age of mothers may be protective against undescended testicles in sons [2, 29, 31, 32].

According to a study by Kjersgaard et al., mothers with overweight and obesity in pregnancy were associated with higher occurrence of cryptorchidism in boys, but a meta-analysis performed by Zhang et al. did not prove this observation [33, 34]. Some studies found an association between cryptorchidism and maternal diabetes [35]. The same meta-analysis by Zhang mentioned before found moderate heterogeneity in studies of the effect of maternal diabetes and cryptorchidism [34].

Damgaard et al. observed that the sons of mothers who regularly consumed at least five drinks per week during pregnancy had ten times greater odds of developing cryptorchidism compared to those not exposed [36]. However, a recent meta-analysis reported no such association [34].

Large meta-analyses reported higher incidence of cryptorchidism among sons of mothers who smoked tobacco during pregnancy. Some authors even observed a correlation between the risk of cryptorchidism and the number of cigarettes smoked per day [34, 37, 38]. It is not debatable that the chemicals in tobacco smoke cause genetic mutation and vasoconstriction and disrupt the endocrine system. It is postulated that paternal smoking could also be associated with cryptorchidism, possibly because of passive inhalation of smoke by the mother and/or damage to the sperm cells [39].

A strong correlation between maternal use of pain killers and undescended testicles in their sons was observed by many authors [40, 41]. Up to 24% of cryptorchidism cases could be attributed to the use of pain killers by mother during pregnancy [40]. Still there are conflicting results with little or no influence of painkillers taken by mothers during pregnancy and undescended testicles in their sons [42, 43].

Studies that have investigated anti-nausea medications, anti-retrovirals, antibiotics, anti-depressives, laxatives, cough medications, anti-anaemics, hypnotics, and anti-epileptics have found little or no association with their use by mothers and cryptorchidism in sons [2, 44–48].

The recreational use of psychoactive drugs by mothers during pregnancy was also investigated, but the association with the risk of cryptorchidism was not found [2, 49].

Subfertility is a known risk factor for congenital malformation in offspring [2]. In the cohort of cryptorchid boys there is a higher representation of mothers who have had intrauterine insemination [1]. Berkowitz et al. found that clomiphene – an oral medication taken during intrauterine insemination – was associated with two-times higher risk of cryptorchidism, but statistical significance was not found [49]. Also diethylstilboestrol, a hormonal contraceptive, was found to be associated with increased risk of undescended testicles [1]. Mothers without problems with fertility had no higher risk of cryptorchidism in their sons [1].

PARITY

Surveys about parity and the risk or cryptorchidism give ambiguous results [2, 30, 50].
According to Schnack et al., the risk of cryptorchidism in male twins was 2.6-fold higher than expected and may be related to the shared intrauterine environment [51].

**HORMONES**

Normal testicular development and descent is dependent on sex hormone balance [1].

**OESTROGEN**

According to Sharpe et al., foetal exposure to high levels of endogenous oestrogen may be associated with maldescent of the testes. Contrary to that observation, some other authors connect cryptorchidism with lower oestrogen levels in mothers’ serum [52, 53].

**TESTOSTERONE**

Testosterone is crucial to testicular descent. Still in the literature there is little or no evidence of the association of low maternal serum levels of testosterone and cryptorchidism [2, 53]. Also, lower testosterone levels in cord blood were not associated with undescended testicles [2, 54, 55].

**HUMAN CHORIONIC GONADOTROPIN**

Placentas of boys born with undescended testicles had lower total hCG levels than in control group, which could reflect lower testosterone production, probably leading to problems with testicular descent [56].

Also, mothers with vaginal bleeding during pregnancy had higher risk of cryptorchidism in their sons [1]. According to Damgaard et al., vaginal bleeding may be an indicator of placenta malfunction, which in turn may affect hCG production [1].

**INSULIN-LIKE FACTOR 3 (INSL3)**

According to some authors, cord blood levels of INSL3 are lower in children born with cryptorchidism [54, 55]. It is postulated that exposure to exogenous endocrine-disrupting chemicals probably decrease concentrations of INSL3 [55].

**AMH**

AMH is secreted by immature Sertoli cells during the eighth week of gestation and is responsible for the regression of Müllerian ducts in the male foetus. Mutations in the AMH receptor cause persistent Müllerian duct syndrome in males and disrupt the descent of the testis [57].

Matuszczak et al. found that “AMH was lower in boys with unilateral cryptorchidism (also found to have smaller testis) when compared with the control group” [57]. In another study, which investigated serum levels of AMH one year after orchidopexy, the authors observed an upward trend in AMH concentration, but it was statistically insignificant [58].

Contrary to the previous findings, Komarowska et al. showed that the levels of AMH, INSL3, and inhibin B were not different in the group of boys with undescended testicles and those in the control group [59].

**ENVIRONMENTAL EXPOSURE**

Many studies have shown that exposure to endocrine-disrupting chemicals, such as bisphenol A, dibutyltin, dioxin, heptachlor epoxide, hexachlorobenzene, polychlorinated biphenyls, and polybrominated diphenyl ethers, interrupt the testicular descent [2, 60–63]. Some other authors did not find such associations [55, 64]. It is postulated that not individual chemicals but the mixture has an effect on testicular descent [65].

Jorgensen et al. (C138) observed that “sons of mothers who farmed during pregnancy were nearly a third more likely to develop cryptorchidism” [66]. Morales-Sucre-Varrela et al. observed the same effect of paternal exposure to heavy metals [67]. Bornman et al. observed that “sons born to women who lived in areas sprayed with dichlorodiphenyltrichloroethane (DDT) were more than twice as likely to be born with undescended testicles” [68].

Czeizel et al. found that the proximity of an acrylonitrile factory increased the risk of cryptorchidism [69]. Kim et al. found the same association between cryptorchidism and living near a petrochemical plant [70].

As for diet, consumption of smoked food during pregnancy seemed to have influence on testicular descent in sons [71]. The evidence for the influence of the caffeine use are conflicting, some authors observed no association, others found positive correlation with cryptorchidism [2, 49, 72].

**GENETIC CAUSES**

A higher than average number of boys with undescended testes have a positive family history of cryptorchidism when compared to healthy controls. Some authors report that 7% of siblings of boys with undescended testes have cryptorchidism [3]. In Denmark “the concordance rates of cryptorchidism were 3.2% in boys with no familial relationship, 3.4% in paternal half-brothers, 6.0% in maternal half-brothers, 8.8% in full brothers, and around 25% dizygotic and monozygotic twins” [73]. These findings stress the importance of the shared intrauterine environment of the twins [73]. There is also evidence of varying risk of undescended testicles depending on the ethnicity, e.g. In the United
States White males have higher incidence of cryptorchidism than Black males [29].

The frequency of genetic alterations in boys with cryptorchidism is reported to be low [74]. The most common genetic findings in boys with undescended testicles were cases of Klinefelter syndrome and mutations in the INSL3 receptor gene [74]. An analysis of the literature shows a 2% prevalence of mutation in the INSL3 gene in cryptorchid boys and mutation in the RXFP2 gene in 4%; these mutations may be more frequent in bilateral cryptorchidism [4, 75–77]. Some authors conclude that the disruption of INSL3, Rxfp2, or AR genes or the gubernaculum mesenchyme alters the testicular descent [4, 75–77]. Also, all genetic disorders responsible for insufficient androgen production can alter descent of the testis.

The AR gene provides instructions for making a protein called an androgen receptor. In an animal model of AR knockout in the gubernaculum, “the males exhibited a suprascrotal cryptorchidism despite normal plasma levels of testosterone” [78]. However, mutations of the AR gene are rarely associated with isolated cryptorchidism [79]. Ferlin et al. reported that “the prevalence of AR mutations was 1.63% in adult men with a history of undescended testis” [74].

According to animal studies The HOXA10 transcriptional factor is implicated in the early embryonic development of the reproductive system, and male knockout mice present bilateral cryptorchidism [4].

In animal studies inactivation of Wilms Tumour 1 (WT1) – a transcription factor expressed in the early embryonic development and differentiation of the renal and gonadal system WT1 in the gubernaculum – caused abnormal differentiation of the gubernaculum, and unilateral cryptorchidism in 40% of animals [80].

The AXIN1 gene encodes a cytoplasmic protein that contains a regulation of G-protein signalling (RGS) domain and a dishevelled and Axin (DIX) domain. The AXIN1 gene is thought to have an impact on migration of the testis because of different repartition of AXIN1 SNPs between cryptorchid and normal boys [81].

According to Hadziselimovic et al., “most cases of isolated cryptorchidism have either a disruption of FGFRs, FGFR1, and FGFR3 and/or a disturbance of the genes involved in the regulation of the hypothalamo-pituitary-gonadal axis” [82].

Cryptorchidism is also associated with several syndromes including abnormal muscle development, e.g. prune-belly, which consists of: cryptorchidism, abdominal wall defects, and genitourinary defects [4]. Also, children with Down syndrome have an increased risk of cryptorchidism [4]. In Noonan syndrome, the occurrence of primary hypogonadism depends on the existence of cryptorchidism, and Prader-Willi syndrome may present with either primary or combined forms of hypogonadism [4].

CONCLUSIONS

Undescended testicle is the most common congenital genital malformation in boys. The aetiology of cryptorchidism is complex with a high probability of genetic predispositions and environmental exposures at the same time playing a role in increasing its risk. Large cohort studies are needed to verify this.

DISCLOSURE

The authors declare no conflict of interest.

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