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(Review Article)



Undescended testis, an often-overlooked problem in newborns: A Literature Review

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Abstract

Undescended testis (UDT) or cryptorchidism is one of the most prevalent congenital abnormalities in male infants. Cryptorchidism is defined as failure of a testis to descend into a scrotal position, or even absent of the testis. For effective reproduction in the future, the testes must descend into the scrotum's lower temperature environment. In addition to being linked to an increased risk of testicular germ cell cancers, poor fertility, and testicular torsion, cryptorchidism can also lead to psychological issues. In developing countries, it is not unusual for patients with undescended testes (UDT) to present in adulthood and the late detection of UDT can be problematic, because of the clinicians are often unaware about genital parts examination in newborn care.

Keywords: Undescended testis; Cryptorchidism; Congenital; Pediatric.

1. Introduction

Cryptorchidism is a common congenital deformity in pediatric urology, commonly known as undescended testis (UDT) or incomplete testicular descent [1]. According to the location of the testis, cryptorchidism is classified as palpable testis and non-palpable testis (NPT), and palpable testis with the former representing greater than 80% of cryptorchidism cases [2]. Cryptorchidism may manifest on one or both sides, but it most usually affects the right testicle. Bilateral cryptorchidism affects approximately 10% of all undescended testicle patients [3]. Approximately 80% of cryptorchid testes descend by the third month adhering to birth. This brings the genuine incidence to roughly 1%. If the testis has not descended by six months of age, it is unlikely to do so spontaneously. Surgical correction should be considered. Treatment for cryptorchidism aims to reduce the risk of reproductive issues, testicular cancer, torsion, and inguinal hernia [4]. Although the etiology of cryptorchidism seems poorly understood, care has developed with the obvious awareness that hormonal treatment is mainly ineffective and that early surgery (before to 1-2 years of age) leads to better testicular outcomes [5].

2. Epidemiology

UDT is a common congenital anomaly, affecting 2-8% of full-term infants and 33-45% of preterm or underweight ($<2500\,\mathrm{gr}$) infants [6]. Most of testes descend within the first 6-12 months, reducing the incidence to 1-2% in boys aged 6 months to 1 year. Seven percent of the siblings of boys with undescended testes have cryptorchidism. Cryptorchidism affects around 1.5% to 4% of fathers and 6% of brothers among individuals with cryptorchidism [4].

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3. Etiology

The etiology of cryptorchidism is mainly unknown, while several theories have been offered. Among others, placental malfunction with lower hCG secretion may be responsible for hormonal and other disorders during the fetal phase of life [7]. A functioning hypothalamic-pituitary-gonadal axis is required for proper testicular descent. Birth weight appears to be the most significant risk factor for undescended testes, followed by family history. The absence of an appendix testis has been associated to abdominal and cryptorchid testes, particularly those positioned close to the external ring. The actual function of the appendix testis in testicular descent is unknown [4]. Testicular descent occurs between 8-15 and 25-35 weeks of gestation, with two hormone-controlled stages. During the fetal phase, both testes may not reach the scrotum in time, resulting in cryptorchidism at birth. Boys with cryptorchidism may nevertheless have spontaneous testicular descent within 6 months of birth. Cryptorchidism has become increasingly common in recent years. Cryptorchidism may be linked to genetics, hormone synthesis and secretion, early birth, pregnancy in older women, and environmental factors. Cryptorchidism affects 18-30% of preterm babies and 0.8-20% of full-term neonates. Unilateral cryptorchidism is a common occurrence [1].

- Risk factors of UDT [3,4]:
 - intrauterine growth restriction (IUGR),
 - prematurity incidence in premature infants 30%,
 - first- or second-born boys,
 - perinatal asphyxia,
 - Cesarean section.
 - toxemia of pregnancy,
- The etiological causes of UDT are usually classified into the following categories [7]:
- Anatomical
- anomalies, including testis, epididymis, and vas deferens.
- the gubernaculum is not properly attached,
- patent processus vaginalis and inguinal hernia.
- Inguinal canal abnormalities are also present.
- Genetic
- androgen receptor gene mutations (chromosome X), i.e. an increased GGN (polyglycine) or CAG (polyglutamine) repeat length.
- heterozygous mutations of Insl3 and Lgr8 genes (chromosome 19) rare in UDT.
- an increased incidence of a polymorphic allele of SF-1 (steroidogenic factor 1), which has a reduced transcription activity. SF-1 may affect expression of INSL3 and LGR8
- Hormonal
- deficient AMH production or insensitivity of AMH receptor,
- deficient INSL3 production or insensitivity of INSL3 receptor,
- deficient GnRH (gonadotropin releasing hormone) and/or gonadotropin production or insensitivity of GnRH or LH receptors,
- · deficient androgen production or insensitivity of androgen receptor,
- deficient CGRP production (disorder of genito-femoral nerves) or insensitivity of CGRP receptor

The underlying causes of UDT are often unknown, despite the previously mentioned criteria. Cryptorchidism may have multiple causes, including genetic, anatomical, hormonal, and environmental variables.

4. Pathophysiology

Testicular descent occurs in two phases, beginning in the eighth week of pregnancy and ending in the third trimester. During the initial trans-abdominal phase, the testicle is directed to the lower region of the abdominal cavity through gubernaculum hypertrophy. The fetal testis produces hormonal substances, including insulin-like 3 protein (INSL3) and androgens, which govern this phase. The second inguinoscrotal phase of testicular descent is dependent on androgens that cause cellular proliferation in the gubernaculum [8].

Temperature is one of the factors contributing to cryptorchid testes' impaired function. It is also possible that temporary hormone deficiencies may cause a lack of testicular descent and affect the formation of spermatogenic tissue [3]. The descent of the testes into the lower temperature environment of the scrotum is critical for future successful reproduction. Cryptorchidism can lead to diminished fertility, higher risk of germ cell tumors, and testicular torsion. It can also cause psychological issues [5]. Men with cryptorchidism are twice as likely to have lower fertility than those

with testes in the scrotum, even after orchidopexy [9, 10]. Bilateral cryptorchidism surgery is expected to reduce fertility in men by 38%, resulting in infertility and azoospermia. Recent evidence suggests that patients with unilateral cryptorchidism have comparable reproductive rates to healthy males [11]. Cryptorchidism can cause spermatogenic tissue degeneration and lower spermatogonia numbers as early as the second year of life [11]. Matuszczak et al. found that rising levels of MMP-1 and MMP-2 in the plasma of boys with cryptorchidism may indicate death of germ cells in undescended testicles due to heat stress. These findings suggest the recommendation for early surgery [12].

5. Clinical Presentation

A testis that is not in the scrotum, known as undescended testis or cryptorchidism, is the most common genitourinary condition in male neonates. Normally, between 25 and 35 weeks of gestation, the testicles descend normally to the scrotum. Diagnoses of undescended testicles occur at birth in 1%–4% of term infants and up to 45% of preterm infants. By three months of age, the testes in many cases of undescended children will naturally descend to the scrotum. It is also possible for testicles to descend after three months of age, particularly in premature babies. On the other hand, the testes may remain in the abdomen or descend only at term in certain premature children. A testis that was in the scrotum may occasionally reascend after delivery [4].

The external genitalia must be inspected thoroughly, especially in patients whose bilateral testes are not palpable. Bilateral impalpable testes can be associated with hormonal failure, conditions such as prune belly syndrome, a posterior urethral valve, abdominal wall defects, or neural tube defects. The patient's groin and scrotum must be palpated from the inguinal canal toward the pubis in a supine or frog-leg position with warm fingers. The inner thigh, femoral, pubic, perineal, and penile regions also must be palpated to find the ectopic testis. Testis can become palpable in a sitting or squatting position but not in a supine position [13].

Testicular regression or vanishing testis are suggested when there is a unilateral impalpable testis accompanied by contralateral compensatory hypertrophy. Testicular regression has been linked to two significant pathogeneses: underlying prenatal endocrinopathy and antenatal vascular accident. Rather than testicular torsion, the cause of antenatal vascular accident is disrupted endothelial cell development and halted endothelial cell migration. Testicular agenesis, in utero infarction, and atrophy of normal testis, leading to vanishing testis or testicular regression, can also be caused by intrauterine gonadal vascular twisting and failure of the intrauterine testicular blood supply. In people with undescended testicles, the prevalence of monorchidism (unilateral absence testis) might reach 4%, whereas that of anorchidism (bilateral absent testes) is less than 1% [14].

A disruption in testicular descent can result in transverse testicular ectopia, an uncommon syndrome when both testes move into one inguinal canal. Transverse testicular ectopia frequently manifests as a contralateral inguinal hernia and unilateral impalpable testis. When the testes are inserted into one hemiscrotum following surgery for an inguinal hernia, the majority of individuals receive this diagnosis [4].

5.1 Classification of Undescended Testis

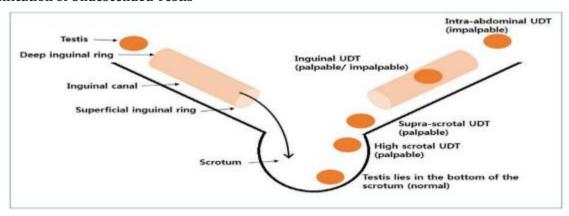


Figure 1 Testicular position, classified as intra-abdominal, inguinal, supra-scrotal, high scrotal, and scrotal according to the process of testicular descent.

Testicular position is classified as intra-abdominal, inguinal, supra-scrotal, high scrotal, and scrotal according to the process of testicular descent. Intra-abdominal testis is not palpable. Inguinal testis is sometimes palpable. Supra-scrotal and high scrotal testes are palpable. Scrotal testis is considered normal, as it lies in the bottom of the scrotum [4].

Testicles that have not descended are categorized according on their existence and placement. When a testis is palpably undescended, it can be felt in the inguinal canal or in an ectopic location, such as the inner thigh, femur, pubic, or perineal areas. The testis in an impalpable undescended testis might be found in the internal inguinal ring, inguinal canal, or abdomen. It might not exist at all. The term retractile testis refers to a testis that has completed its descent and is discovered in the scrotum, occasionally in a suprascrotal position. It can be gently pulled to the bottom of the scrotum, where it may remain for some time. This is commonly accepted as normal. However, up to one-third of retractile testis can reascend and become undescended, which is not considered normal. A percentage of cases of undescended testis are reascended testis, in which a previously descended testis ascends to a higher location. Rescended testis may result from nonorthotopic gubernacular insertion (higher insertion), patent processus vaginalis, and an unusually prolonged fibrotic remnant of the processus vaginalis [4].

Diagnostic guidelines of undescended testes	AUA	BAPS/BAUS	CUA	EAU
Surgical specialist referral	If there is no descent by 6 months,	If there is no descent by 6 months.	If there is no descent by 6 months,	If there is no descent
	or if UDT is newly diagnosed >6		or if UDT is newly diagnosed >6	by 6 months.
	months of age.		months of age.	
Endocrine assessment for bilateral UDT	Recommended	Recommended	Recommended	Recommended
Diagnostic exploratory laparoscopy for impalpable UDT	Recommended	Recommended	Recommended	Recommended
Imaging study	Not recommended	Not recommended	Not recommended	Not recommended

Figure 2 Diagnostic guidelines of undescended testis

Ultrasonography was unable to identify impalpable testes or detect whether a testis was present in a systemic review. Additionally, an intra-abdominal testis could not be ruled out. Similarly, the diagnostic accuracy of magnetic resonance imaging or ultrasound in determining the presence or absence of intra-abdominal testis is low in situations of impalpable undescended testis. Although ultrasonography is not intrusive, the AUA, BAPS/BAUS, CUA, and EAU recommendations do not advocate use because it cannot improve diagnosis accuracy or alter treatment [15].

Before and after orchiopexy, some practitioners assess undescended testicles using ultrasound. In practical terms, ultrasonography is utilized due to diagnosis uncertainty. The majority of Korean urologists conducted diagnostic imaging scans for unilateral impalpable undescended testis, according to a nationwide questionnaire outlining the practice patterns of undescended testis in Korea that was issued to 167 urologists in Korea. While 40% carried out both ultrasonography and additional imaging tests like computed tomography or magnetic resonance imaging, 52% of the participants only performed ultrasonography. Imaging investigations were recommended since they could provide objective evaluations of testicular size before and after surgery and assist with any post-orchiopexy legal issues. Merely 8% refrained from conducting imaging studies, arguing that the outcomes of such studies cannot alter care and that diagnostic exploratory laparoscopy is inevitably necessary [15].

6. Management of Undescended Testis

MANAGEMENT	AUA	BAPS/BAUS	CUA	EAU
Hormonal therapy	Not recommend	Not discussed	Not recommend	Not recommend
Age at orchiopexy	If no descent by 6 months, surgery should be done within the next year.	6-18 months of age	6-18 months of age	6-12 months of age (<12 months of age, by 18 months at the latest)
Fertility	Decreased fertility and paternity in bilateral UDT	Not discussed	Decreased paternity in bilateral UDT	Decreased fertility and paternity in bilateral UDT, age at orchiopexy is important.
Testicular cancer	Increased risk in intra-abdominal UDT, decreased risk in orchiopexy before puberty (compared to orchiopexy after puberty)	Not discussed	before puberty, but still above	Increased risk of testicular cancer, decreased risk in orchiopexy before puberty (compared to orchiopexy after puberty)
Self-examination after puberty	Recommended (manthly)	Not discussed	Recommended, no need for longterm urological follow-up	Recommended

Figure 3 Guidelines on management of undescended testis

It is not advised to do a routine endocrine assessment on a unilaterally undescended testis. According to guidelines from the American Urological Association (AUA), the British Association of Pediatric Surgeons/British Association of Urologic Surgeons (BAPS/BAUS), the Canadian Urological Association (CUA), and the European Association of Urology (EAU), an endocrine assessment is necessary for bilateral undescended testes. The gold standard with high sensitivity and specificity for identifying impalpable undescended testis is diagnostic exploratory laparoscopy [15].

6.1. Medical Treatment

- According to the AUA Guidelines, "Since there is insufficient evidence for long-term efficacy and low response rates, providers should not use hormonal therapy to induce testicular descent."
- Hormone therapy is advised by the American Pediatric Association Guidelines in cases of undescended testicles linked to Prader-Willi syndrome. They contend that in order to avoid general anesthesia in newborns with low muscle tone and a high risk of underlying respiratory impairment, a therapeutic trial with human chorionic gonadotropin (HCG) is indicated for the treatment of undescended testes prior to surgery.
- Human chorionic gonadotropin (HCG) is the hormone that is used the most frequently. The undescended testicle's condition is reevaluated after a series of HCG injections. The stated success rate ranges from 5% to 50%.
- In addition to confirming Leydig cell responsiveness, hormone therapy causes a small penis to develop more as a result of elevated testosterone levels.

The cost of hormone treatment is less than surgery, and the chance of complications is minimal. However, a recent metaanalysis of seven randomized clinical trials concluded that hormonal therapy was no more effective than a placebo [10].

6.2. Surgery

Surgery is recommended for congenital undescended testes between the ages of 6 and 18 months. Many experts recommend surgery early, at around six months, to optimize testicular growth and fertility. For premature babies, corrected age is used to determine optimal surgical timing. The longer the cryptorchid testis remains untreated, the greater the germ cell loss and the decrease of fertility which is why early orchidopexy is the usual, standard remedy. Adult orchidopexies patients with bilateral undescended testes are nearly usually azoospermic and infertile, yet there are currently a few anecdotal accounts of assisted reproduction pregnancies in this population. Surgery is advised soon after diagnosis for acquired (testis confirmed normal prior to diagnosis) and entrapped (after hernia repair) undescended testes. A yearly physical examination is advised for retractile testes due to the 2% to 50% stated chance of a retractile testis developing into an acquired undescended testis [16].

6.3. Technique of Orchiopexy

For palpable undescended testes, an inguinal or scrotal orchiopexy is recommended.

- An incision is made in the high scrotum, median scrotal raphe, high edge of the scrotum, or groin. Many different types of retractors can be used depending on the incision size. Inguinal incisions can be as small as 1 cm. Scrotal incisions can be larger as they tend to heal concealed, especially when in the median raphe.
- The testis can be approached first or the cord first; for scrotal cases, the testis is found first. For an inguinal approach, the testis can be approached first, or the external oblique fascia opened proximal to the external ring, and the cord approached first.
- When approaching the testis first, all the cremasteric muscles are divided, as well, as everything is not going into the external ring.
- The more difficult part of the case is separating the hernia sac from the vas and testicular vessels. This can be approached anteriorly or posteriorly. The posterior approach is much easier to teach and learn.
- How the testis is positioned and secured in the scrotum varies. Most would agree that a sub-dartos pouch is
 desirable. Some surgeons do not suture the testis in place, while others use either absorbable or non-absorbable
 sutures. Some will just close the passage into the groin.

For nonpalpable testes under anesthesia, exploratory laparoscopy is recommended. If a testis is found during exploratory laparoscopy, the options are [16]:

- Laparoscopic orchiopexy preserving the vessels: the testis is dissected off a triangular pedicle containing the gonadal vessels and the vas.
- Laparoscopic one-stage Fowler Stevens (FS) orchiopexy: the gonadal vessels are divided, and the testis is dissected off a pedicle of the vas and brought down in one stage.

- Laparoscopic two-stage Fowler Stevens orchiopexy: the vessels are divided with clips, but dissection of the testis is postponed for six months to allow for optimal development of collaterals.
- Laparoscopic two-stage traction-orchidopexy (Shehata technique): the intrabdominal testis is fixed to a point one inch (2 cm) medial and superior to the contralateral anterior superior iliac spine, which provides traction. The testis is left there for three months, after which a laparoscopy-assisted ipsilateral subdartos orchidopexy is performed. This technique is an alternative to the two-stage Fowler Stevens orchidopexy. Its main advantage is that it allows an intraabdominal testis to be relocated into the scrotum without the need to sacrifice the main testicular vessels. It should be considered whenever a single-stage laparoscopic orchidopexy cannot be performed due to inadequate length. It provides a very high success rate with the preservation of testicular vasculature without atrophy. Overall success with this technique is from 84% to 100%.

If no testis is found during exploratory laparoscopy, one must determine the presence of either blind-ending vessels or a testicular nubbin to completely rule out a missing testis. The vas can be dissociated from the testis and thus is not always a good guide to finding the gonad [17].

If the internal ring is closed, but vessels are going into it, a scrotal exploration usually will find a testicular nubbin. It will appear as a small structure with a brown spot.

If vessels are going into an open inguinal ring, one can usually push the testis into the abdomen, but if not, an inguinal or scrotal exploration is warranted.

7. Differential Diagnosis

Other problems to be considered include the following retractile testis, anorchia, intraabdominal testis and vanishing testis syndrome or nubbin testicle resulting from perinatal torsion. The differential diagnosed also can be considered based on their mal-position according to the process of testicular descent [18]. Differentiating between a testicle that is retractile and one that is not naturally descending into the scrotum presents a common diagnostic issue. Compared to undescended testes, retractile testes are more prevalent and don't need to be surgically corrected. In healthy guys, the testicles retract into the inguinal canal and upper scrotum when the cremaster muscle contracts. In newborns, this response is more active.

It is challenging to differentiate between a retractile testicle located in the lower inguinal canal and one high in the scrotum. The cross-legged stance, soaping the clinician's fingers, and inspecting the patient in a warm bath are among the identification-aiding maneuvers.

The American Urological Association (AUA) Guidelines define a retractile testis as "...one that is initially extra-scrotal on examination or moves easily out of the scrotal position, (often associated with a vigorous cremasteric reflex), but that can be manually replaced in a stable, dependent scrotal position and remain there without tension at least temporarily." [19].

8. Prognosis

The prognosis is excellent when diagnosed and treated appropriately. Infertility and the risk of testicular cancer are still slightly higher than in the general population [20]. However, a recent Danish study of over 6,000 men suggested testicular hypofunction, smaller testis volume (by 3.5 cc), 28% reduction in sperm concentration, and reduced Leydig cell function in men with a history of cryptorchidism compared to normal men [21].

9. Complications

Patients with undescended testicles have a higher risk of testicular cancer than the general population. The age at orchiopexy and the initial location of the testes are predictive markers for later-life cancer and fertility [4]. Complications regarding surgical management, such as orchiopexy are testicular ascent and atrophy as the two main consequences linked to orchiopexy. These happen in approximately 1% of cases with palpable testes. The rate for laparoscopic orchiopexies is approximately 5%. Testicular atrophy rates following one or two step Fowler-Stephens orchiopexies (splitting the vessels) range from 20% to 30% (worse for the one-stage surgery). One of the most serious side effects of orchiopexy is testicular loss brought on by spermatic cord over skeletonization.

10. Conclusion

Cryptorchidism is a common congenital abnormality in newborns. The diagnosis of cryptorchidism is often missed at the beginning. When providing first neonatal care, doctors frequently neglect to examine the baby's external genitalia. In addition, the baby's parents frequently pay little attention to it or are unaware of it, which delays the identification and treatment of undescended testis. It is also important to note that cryptorchidism is often associated with other congenital disorders. Therefore, we, the clinicians, must have more knowledge and attention to be able to educate the parents of infants.

Compliance with ethical standards

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Disclosure of Conflict of interest

The authors declare no conflict of interest.

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