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UNDESCENDED TESTIS – CURRENT CONCEPTS

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ABSTRACT

Undescended Testis (UDT) is a common congenital anomaly especially in preterm boys. Serial examination is essential to diagnose cases of acquired cryptorchidism. The treatment of UDT has undergone a dramatic change in recent times with emphasis on early surgical intervention between 6 months to 1 year of age. Hormonal therapy to induce descent of testes has been used for over 70 years based on the premise that androgens promote testicular descent, but efficacy is questionable. The traditional approach to surgical treatment of palpable testes is inguinal orchidopexy. Laparoscopy has become a valuable tool in cases of nonpalpbale testis. The current concepts in the management of UDT are reviewed.

INTRODUCTION

Cryptorchidism is one of the most common congenital anomalies, occurring in 1% to 4% of full-term and 30% of preterm newborn boys (Sijstermans *et al*., 2008).Perinatal risk factors most consistently associated with cryptorchidism include prematurity, low birth weight or small size for gestational age, breech presentation, and maternal diabetes (Damgaard *et al*., 2008). The majority of congenital undescended testis (UDT) descend spontaneously during first 3 months of life. Spontaneous descent occurs secondary to a temporary testosterone surge during first 2 months which also results in significant penile growth. The reported frequency of spontaneous testicular descent after birth varies among series from 50 to 87%, likely because of variable inclusion of boys with high scrotal testes (Berkowitz *et al*., 1993). The cryptorchidism is bilateral in 10 % of cases. Acquired cryptorchidism, or testes that are diagnosed as cryptorchid after apparent full descent at birth or in the neonatal period, is now fully accepted as a clinical entity (Barteczko *et al*., 2000). Acquired undescended testes are diagnosed at an average age of 8 to 11 years and are more commonly in a lower position, associated with a closed processus vaginalis and normal epididymis, than in cases diagnosed as congenital.

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The reason for a later diagnosis remains unknown; theories include presence of a fibrous remnant of the processus vaginalis that tethers or foreshortens the cord over time or mobility of the test is within an open sac (Barthold, 2008). These testes may be highly mobile and initially appear descended until somatic growth results in relative widening of the distance between testis and scrotum. A diagnosis of acquired cryptorchidism may be more likely in boys with retractile testes, although testis retractility is common in normal populations. In a hospital-based study of unselected boys, the testis was initially suprascrotal on examination (retractile) in up to 30% of boys at 4 years and10% of boys 4 to 12 years of age but was intrascrotal in all boys over the age of 12 (Keys, 2012). Therefore, careful serial physical examination is recommended to accurately determine testicular position and identify cases of acquired cryptorchidism in boys with retractile testes (Redman, 2005).

Descent of Testis

Testicular descent is a complex and prolonged gestational event. At 7-8 weeks of gestation, testes start developing in abdominal cavity. At 10-11 weeks, Leydig cells produce testosterone which stimulates differentiation of Wolffian (mesonephric duct) into epidydimis, vas deferens, seminal vesicles and ejaculatory ducts (Abeyaratne *et al*., 1969). The process of testicular descent is regulated by an interaction between hormonal and mechanical factors including testosterone, dihydrotestosterone, mullerian-inhibiting factor,

gubernaculum, intraabdominal pressure, genitofemoral nerve and by two Leydig cell hormones—insulin-like 3 (INSL3*)* via its receptor relaxin/insulin- like family peptide receptor 2 (RXFP2), and androgens via the androgen receptor (AR) (Svechnikov, 2008).

Descent of testis is described in 2 phases:

- Transabdominal migration, and
- Inguinoscrotal descent.

Both phases occur at different times and are under different hormonal control.

- The first phase of testicular descent occurs between 10-15 weeks of gestation and is caused by growth and enlargement of gubernaculum described by Wensing in 1973 as swelling reaction (Lemeh, 1960). The main hormone responsible is insulin like 3 (INSL3).
- The second phase occurs between 25 -35 weeks of gestation and mainly androgens are responsible.Just below the lower pole of testis, peritoneum herniates as a diverticulum along anterior aspect of gubernaculum, eventually reaching scrotal sac known as Processus Vaginalis (PV). Testes remain along abdominal end of inguinal canal up to 7 months. It then passes through inguinal canal behind PV. Normally it reaches scrotal sac by end of 8 months.

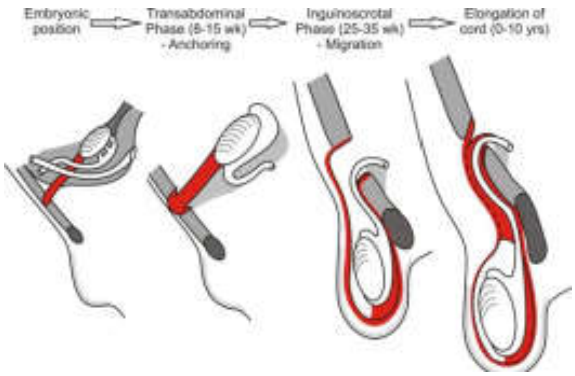


Fig. 1. Testicular descent – Role of gubernaculum and processus vaginalis

Reactivation of the hypothalamic-pituitary-gonadal (HPG) axis occurs during the neonatal period, a phenomenon known as "mini-puberty". The postnatal hormone surge is accompanied by increased testicular volume, primarily as a result of Sertoli and germ cell proliferation Sertoli cell proliferation continues in the first year of life and is a major determinant of ultimate testicular size (Sharpe *et al*., 2003).

Definition of terms

Normal scrotal position has been defined as positioning of the midpoint of the testis at or below the midscrotum. *Undescended testis* or *cryptorchidism* is the absence of one or both testes in normal scrotal position and during initial clinical evaluation may refer to palpable or nonpalpable testes, which are either cryptorchid or absent. Most absent testes are *vanishing* or *vanished*, being present initially in development but becoming lost as a result of vascular accident or torsion unilaterally *(monorchia)* or, very rarely, bilaterally *(anorchia).*

Acquired cryptorchidism is defined as cryptorchid testes that were documented as scrotal at a previous examination without intervening inguinal surgery. *Retractile testes* are scrotal testes that retract easily out of the scrotum but can be manually replaced in a stable scrotal position and remain there at least temporarily until there is recurrent stimulation. Passage of the testis into the inguinal canal rarely occurs before 22 weeks in the human fetus, and the majority of testes are scrotal after 27 weeks; time spent in the inguinal canal seems to be limited for the majority of human fetal testes. Population-based studies suggest that the maternal environment may contribute to the risk of cryptorchidism, but it remains unclear if risk is related to maternal exposures, characteristics, or lifestyle. Maternal alcohol consumption or binge drinking was associated with cryptorchidism in some studies but not others (Barthold, 2008). A review of data for maternal smoking confirms inconsistent results but suggests that a small-to-moderate increased risk for cryptorchidism is present in offspring. Parental occupation is not consistently associated with cryptorchidism in offspring, although some data suggest increased risk in horticulture-related professions (Barthold, 2008).

Testicular dysgenesis syndrome is the term used to describe a potentially related constellation of reproductive abnormalities including cryptorchidism, hypospadias, infertility, and TGCT.[9] The proposed cause is a deficiency in fetal androgen production resulting from exposure to endocrine- disrupting chemicals (EDCs). Because multiple genetic and environmental factors likely contribute to cryptorchidism, identification of risk factors is difficult in case-control studies. Certain anomalies are associated with increased risk of cryptorchidism. These include all cases of classic prune-belly (triad or Eagle-Barrett) syndrome, 80% of spigelian hernia, 41% to 54% of cerebral palsy[12], 38% of arthrogryposis, 15% of myelomeningocele, 16% to 33% of omphalocele, 5% to 15% of gastroschisis, 19% of imperforate anus, 12% to 16% of posterior urethral valve, and 6% of umbilical hernia patients (Barthold, 2008).

Diagnosis

To best determine testicular position, boys should be examined in the supine and, if possible, upright cross-legged and standing positions. Abduction of the thighs contributes to inhibition of the cremasteric reflex, which is elevation of the testis that is elicited by scratching the inner thigh. The examination should include documentation of testicular palpability, position, mobility, size, and possible associated findings such as hernia, hydrocele, penile size, and urethral meatus position. Patient distraction, a warm room and hands, use of liquid soap on the examiner's hands, and repeated examinations also help to localize the testis. Scrotal asymmetry can be a useful clinical sign because it is commonly present in boys with unilateral cryptorchidism (Snodgrass *et al*., 2011). In large clinical series, the majority (75% to 80%) of undescended testes are palpable and 60% to 70% are unilateral; involvement of the right side is more common overall but less frequent in series of nonpalpable testes. In a meta-analysis of surgical patients, testes were abdominal in 34%, near the internal ring ("peeping") in 12%, canalicular in 27%, and beyond the external ring in 27% (Thorup *et al*., 2011a).

Table 1. Classification of Cryptorchidism

Type	Description	Incidence %
Hypoplastic or absent testis	Testis never develops (agenesis) or disappears after intrauterine torsion (anorchia)	3-5
Undescended testis	Testis whose descent stopped before reaching scrotum	
	*Abdominal retention-(intra-abdominal testis above internal ring)	5
	*High Inguinal retention (peeping)-testis at level or just above internal ring	15-20
	*Low Inguinal retention (canalicular)-testis in canal or above outer ring	30-35
	*Gliding –testis can be brought to upper scrotum but retracts once released	5-10
Ectopic testis	Testis whose descent took a wrong direction • Perineal • Crossed • Penis root • Crural	2
Retractile testis	Descended Testischanging its position	30
Acquired cryptorchidism	Testis no longer palpable in scrotum after normal descent	

Comparison between Undescended testis and Ectopic testis

Undescended Testis	Ectopic testis
Testis is arrested in its normal path of descent	Testis deviates from its normal path of descent
Usually underdeveloped	Fully developed testis
Undeveloped and empty scrotum on affected side	Empty but usually fully developed
Shorter length of spermatic cord	Longer length of spermatic cord
Poor spermatogenesis after 6 yrs.	Spermatogenesis is perfect
Usually associated with indirect hernia	Never associated with indirect inguinal hernia
Associated with number of complications	Liability to injury

Associated genital findings may warrant additional diagnostic studies that are best completed in the neonatal period. If neither testis is palpable, particularly if penile development is abnormal, karyotype and hormonal analyses are performed urgently to rule out congenital adrenal hyperplasia and obviate the potential adverse effects of undiagnosed salt wasting. Routine circumcision should be delayed until evaluation confirms a genetically normal male. Hypospadias is associated with cryptorchidism in 12% to 24% of cases. Micropenis was reported in 46% of boys with anorchia caused by bilateral vanishing testes also called *testicular regression syndrome*, and small penile size in association with cryptorchidism is also observed in cases of hypogonadotropic hypogonadism.

Palpable Testes

Undescended testes may be located along the line of normal descent between the abdomen and scrotum or in an ectopic position that is most commonly the SIP (Superficial Inguinal Pouch, anterior to the rectus abdominus muscle) or, more rarely, in a perirenal, prepubic, femoral, peripenile, perineal, or contralateral scrotal position. Every effort should be made by the examiner to determine the lowest position the testis may attain. Manual downward pressure with one hand along the ipsilateral inguinal canal from the anterior iliac spine to the scrotum and palpation with the opposite hand helps to identify the lowest position of a palpable testis. The gold standard for diagnosis remains careful examination of a child in several positions and confirmation of incomplete descent of the testis to a dependent scrotal position after induction of anesthesia.

Nonpalpable Testes

When a testis is nonpalpable, possible clinical findings at surgery include (1) abdominal or transinguinal "peeping" location (25% to 50%), (2) complete atrophy (vanishing testis, 15% to 40%), and (3) extra-abdominal location but nonpalpable testis because of body habitus, testicular size, and/or limited cooperation of the patient (10% to 30%). If both testes are nonpalpable and not distal to the internal inguinal ring in a genetic male, at least 95% are abdominal, with cases of bilateral vanishing testis occurring rarely. Diagnosis of a vanishing testis requires documentation of blind-ending spermatic vessels in the abdomen, inguinal canal, or scrotum. Endocrine evaluation in cases of suspected bilateral vanishing testes (anorchia) shows elevated basal serum gonadotropin levels and no response to hCG stimulation.

Because hCG stimulation testing is not well standardized and has the potential for side effects and inaccuracy, it is no longer the procedure of choice for documentation of anorchia (Zenaty *et al*., 2006). Inguinoscrotal ultrasonography and magnetic resonance imaging (MRI) are not usually helpful and are not recommended in the evaluation and management of a nonpalpable testis. Imaging is not indicated for diagnosis of the nonpalpable testis, because it has limited accuracy and does not obviate the need for definitive surgical intervention. Diagnostic laparoscopy, followed by laparoscopic orchidopexy if an abdominal testis is present, has become the preferred approach to the nonpalpable testis for many clinicians. Laparoscopy is preceded by an examination under anesthesia, which may be a useful adjunct that helps to define the appropriate course of action. Although laparoscopy does not always provide a direct diagnosis, in many cases it either provides visualization of the testis or guidance for the surgeon's next steps.

Important laparoscopic observations include the size and position of the spermatic vessels and vas; testicular size, quality, and position if visible; and patency of the internal inguinal ring. The combination of a closed internal ring and a blind-ending spermatic artery and vas confirms an abdominal vanishing testis. Therefore, if laparoscopy does not unequivocally localize the testis or blind-ending spermatic artery, additional surgical exploration is needed for definitive diagnosis. This may be performed laparoscopically after the placement of additional working ports. Laparoscopy is the procedure of choice to confirm or exclude the presence of a viable or remnant abdominal testis, unless a prominent scrotal nubbin is palpable with other clinical signs of monorchism.

Table 2. The scrotum has become a highly specialized, low-temperature environment

Character	Physiological role
Thin, pigmented skin	Heat loss by conduction/radiation
No subcutaneous fat	Heat loss by conduction
Absent hair/fur (e.g. bull/rat)	Heat loss over caudal epididymis
Pampiniform plexus	Countercurrent heat exchange
Cremaster muscle	Controls testicular position in response to external temperature
Dartos muscle	Controls scrotal dependency in response to external temperature
Fat pad in inguinal canal (e.g. rat)	Insulates testis from abdominal cavity
Fat pad between testis and epididymis (rat)	Insulates caudal epididymis from testis
Processus vaginalis closure	Keeps testis outside abdominal cavity

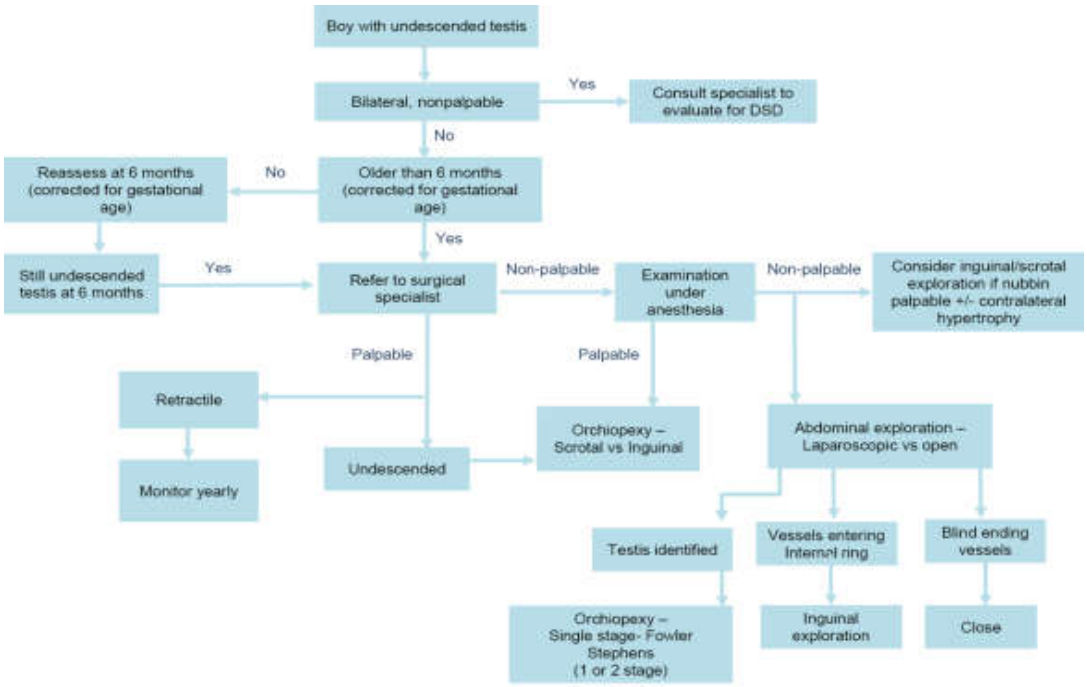


Fig. 2. Algorithm for management of UDT

Effects of Cryptorchidism

Abnormal germ cell development is often present after early infancy in cryptorchid testes. The degree of pathology was similar in true ectopic, SIP, and ascending testes. Postoperative testicular growth was superior in boys who underwent orchidopexy at age 9 months as compared with those randomized to surgery at age 3 years. Cryptorchidism is associated with both primary and secondary effects on testicular development, and the extrascrotal position of the testis may have adverse effects even in infancy. The secondary effects seen in UDT are thought to be caused by the increased temperature of the UDT compared with its scrotal counterpart. The scrotal testis resides in a specialized low-temperature environment with heat-exchange mechanisms in the pampiniform plexus, pigmentation of the scrotal skin, absence of subcutaneous fat, and regulation by temperature-sensitive muscles, i.e. the cremaster and dartos muscles. In the human, the scrotal testis is at 33 °C compared with an inguinal testis which is at approximately 35 °C and the intra-abdominal testis at 37 °C. On an evolutionary time scale, the testis has descended into this specialised external, low-temperature environment for advantages in sperm storage, particularly in the epididymis. The 120 million years which has elapsed since the testis first descended in primitive mammals has allowed ample time for adaptation of the physiological mechanism within the postnatal testis to this special environment. It is not surprising, therefore, that in UDT the secondary increase in the ambient temperature of the testis leads to progressive dysfunction.

Most enzymes and cellular mechanisms within the testes appear to be well adapted to this lower-than-normal body temperature. Significant derangement of germ cell development in cryptorchid testes begins postnatally, although the changes in testicular physiology that normally occur to adapt to the lower temperature are not known, but it is expected to be in the first few weeks after birth. The abnormally high temperature of the cryptorchid human testis is considered by many authors to be the main or additional cause of this germ cell maldevelopment. Considerable studies have been performed in various animal models showing that heat stress leads to a combination of both indirect and direct effects on the germ cells, causing impaired transformation and maturation as well as affecting apoptosis. This thermal injury is mediated by reactive oxygen species and certain heat-shock proteins, which damage the germ cells as well as Sertoli cells.

Consequences of cryptorchidism are:

- poor testicular growth,
- infertility,
- testicular malignancy,
- associated hernia, torsion of the testis, and
- the possible psychologic effects of an empty scrotum.

Although there is strong evidence that a history of cryptorchidism is associated with subfertility in individual patients, the effects of age at diagnosis, type of treatment, and/or severity of disease on outcome remain incompletely defined. Major limitations in the interpretation of

cryptorchidism outcome studies include selection bias resulting from incomplete follow-up of large patient cohorts and heterogeneity of diagnosis and timing/type of treatment. A history of cryptorchidism is associated with a twofold to fivefold increased risk of testicular cancer.

Management

Surgical correction of cryptorchidism is indicated to optimize testicular function, potentially reduce and/or facilitate diagnosis of testicular malignancy, provide cosmetic benefits, and prevent complications such as clinical hernia or torsion
An algorithm has been established and published as part of the American Urological Association (AUA) cryptorchidism guideline (Kolon, 2014). In infants, observation is indicated for the first 6 postnatal months to allow spontaneous testicular descent. If spontaneous testicular descent does not occur, surgical treatment after 6 months of (corrected gestational) age is indicated. Support for this approach is based on the following rationale: (1) Spontaneous descent is unlikely in full-term males after age 6 months (2) testicular growth is restored after early orchidopexy, and (3) orchidopexy for abdominal testes may be facilitated in young infants, soon after the hormonal surge. After spontaneous testicular descent, continued observation is needed because of the risk for recurrent cryptorchidism or testicular reascent.

Medical Therapy

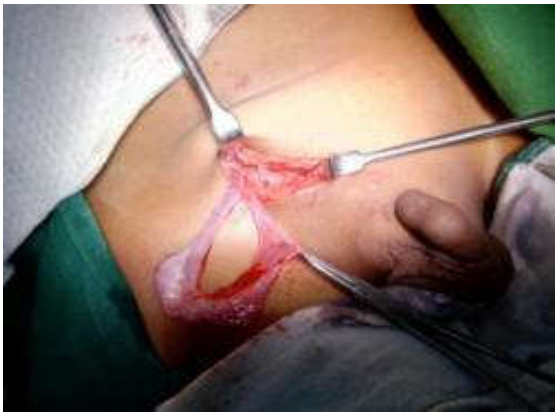
Hormonal therapy has been used for a variety of indications in patients with cryptorchidism, including differentiation of retractile from true undescended testes, stimulation of testicular descent or germ cell maturation, and as an adjunct to abdominal orchidopexy. Hormone therapy is not currently recommended, given the lack of rigorous data supporting its efficacy.[39] Luteinizing hormone–releasing hormone (LHRH) and/or hCG has been used as hormonal therapy to induce descent of testes for over 70 years based on the premise that androgens promote testicular descent, but efficacy is questionable. Hadziselimovic and colleagues have advocated use of low-dose, long-term (every other day for 6 months) LHRH analogue (buserelin) therapy for stimulation of germ cell development (Thorsson *et al*., 2007).
Surgical Approach to the Palpable Testis

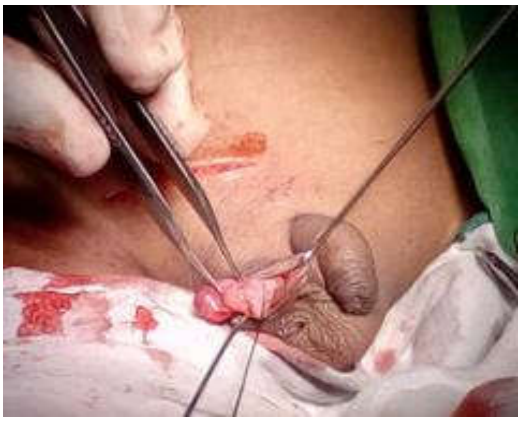
Timing of Surgery

The recommendation that surgical intervention proceed once failure of spontaneous descent is confirmed is now standard. Despite this, the average age at which orchidopexy is performed remains approximately 4 years in many series. The reason for delayed intervention likely reflects a combination of factors, primarily including delayed referral of congenital cases and the occurrence of acquired cryptorchidism. Cases of congenital cryptorchidism may go undetected or untreated in infancy owing to prematurity or other morbidity, may undergo longer than necessary observation for spontaneous descent, or may represent cases of undetected reascent after spontaneous descent in infancy. Delay may also be exacerbated by difficulty in distinguishing undescended from retractile testes (Chan *et al*., 2014). The traditional approach to surgical treatment of palpable testes is inguinal orchidopexy (Docimo, 1995) with repair of an associated hernia if present, although a primary scrotal approach as originally described and advocated by Bianchi and colleagues is an alternative approach (Bianchi, 1989). An option for pubertal and postpubertal boys is orchiectomy, especially if the testis is abdominal or difficult to mobilize because poor spermatogenesis and hypotrophy are usually present and the risk of CIS and torsion exist. A minimum of 6 months' follow-up is recommended to determine postoperative testis position and size. Long-term follow-up should be considered for counseling of the patient regarding fertility issues, risk of testicular malignancy, and self-examination. Torsion of a scrotal testis after orchidopexy has been reported but is very rare, and the risk may be minimized by routine extravaginal testicular fixation in a subdartos pouch. Implantation of a testicular prosthesis should occur at least 6 months after any scrotal procedure or after puberty and is best performed through an inguinal approach. Reoperation is indicated if a testis is nonscrotal after orchidopexy. The importance of correcting a persistently patent processus vaginalis and/or of adequate retroperitoneal mobilization of the cord in cases of high recurrent cryptorchidism has been stressed.

Nonplapable testis

Once an abdominal testis has been identified, the surgeon must decide whether to proceed with an open or laparoscopic, one- or two-stage orchidopexy with possible spermatic vessel transection. Orchiectomy is appropriate for patients with testes that are poorly viable and/or at higher risk for tumor, which may include testes in postpubertal patients or very small or dysgenetic testes in postpubertal patients, and is in our opinion best performed laparoscopically. Operative laparoscopy emerged over 15 years ago as the procedure of choice for abdominal orchidopexy and the basic surgical approach and high success rates have stood the test of time. The feasibility of primary versus Fowler-Stephens orchidopexy depends on the length of the vas and vessels, presence or absence of looping ductal structures, and age of the patient. For testes that are not near (variably defined as 2 to 4 cm above) the internal inguinal ring, transection of the spermatic vessels as originally described by Fowler and Stephens may be necessary; a long-looping vas facilitates but is not required for testicular mobilization to the scrotum.[21] The Fowler- Stephens procedure is now typically performed laparoscopically with spermatic vessel clipping followed by laparoscopic or open testicular mobilization in the same setting, or in a staged approach 6 months later.





Risk of Testicular Germ Cell Tumor (TGCT)

The increased risk of TGCT in males with a history of cryptorchidism has been known for many years. Both seminoma and nonseminomatous germ cell tumors (NSGCTs) develop from CIS of the testis, also called i*ntratubular germ cell neoplasia, unclassified* (ITGCNU), and are believed to be developmental in origin. A history of cryptorchidism is associated with a twofold to fivefold increased risk of testicular cancer. Men with a history of cryptorchidism comprise about 10% of those with TGCT.

- Asymmetry of scrotum is a useful clinical sign
- Meticulous operative technique is essential to separate testis up to internal inguinal ring
- Dissection of hernia sac from the testis
- Routing the testis to scrotum
- Fixation of testis in subdartos pouch

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