



Review Article

Management of undescended testes: European Association of Urology/European Society for Paediatric Urology Guidelines



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Summary

Context

Undescended testis is the most common endocrinological disease in the male newborn period. Incidence varies between 1.0% and 4.6% in full-term neonates, with rates as high as 45% in preterm neonates. Failure or delay of treatment can result in reduced fertility and/or increased testicular cancer risk in adulthood.

Objective

To provide recommendations for the diagnosis and treatment of boys with undescended testes which reduce the risk of impaired fertility and testicular cancer in adulthood.

Evidence acquisition

Embase and Pubmed were searched for all relevant publications, from 1990 to 2015 limited to English language. Data were narratively synthesized in light

of methodological and clinical heterogeneity. The risk of bias of each included study was assessed.

Evidence synthesis

There is consensus that early treatment, by 18 months at the latest, for undescended testes is mandatory to avoid possible sequelae regarding fertility potential and cancer risk. The current standard therapy is orchidopexy, while hormonal therapy is still under debate. However, in some individuals the successful scrotal placement of previously undescended testes may not prevent potential negative long-term outcomes regarding fertility and testicular malignancy.

Conclusions

There is good evidence for early placement of undescended testes in the scrotal position to prevent potential impairment of fertility and reduce the risk of testicular malignancy. No consensus exists on the various forms of hormonal treatment, which are assessed on an individual basis.

Methodology

The scientific literature on congenital diseases is limited. Generally, the level of evidence is poor, with most studies being retrospective with very heterogeneous and not well-defined patient groups and poor stratification of quality. These guideline recommendations were developed by the European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) Guidelines Committee to provide a practical approach for treatment of children suffering from undescended testes. The Embase and Pubmed databases were searched for all relevant publications from 1990 to 2015. The terms cryptorchidism, undescended testis, hormonal treatment, orchidopexy, laparoscopy, testicular cancer,

and fertility were used. At least two reviewers screened all 908 articles independently. Disagreement was resolved by a third party. A total of 73 full-text articles were included in the final version. Key historical articles were also included, for example [1]. The criteria used for level of evidence (LE) and grade of recommendation (GR) were defined according to the widely adopted classification system from the Oxford Centre for Evidence Based Medicine [2] (Tables 1 and 2).

Background

Cryptorchidism or undescended testis is one of the most common congenital malformations in male neonates and is related to a multifactorial process. Incidence varies and depends on

Table 1 Summary of evidence.

	LE
An undescended testis justifies treatment early in life to avoid loss of spermatogenic potential.	2a
A failed or delayed orchidopexy may increase the risk of testicular malignancy later in life.	2a
The earlier the treatment, the lower the risk of impaired fertility and testicular cancer.	2a
In unilateral undescended testis, fertility rate is reduced whereas paternity rate is not.	1b
In bilateral undescended testes, fertility and paternity rates are impaired.	1b
The treatment of choice for undescended testis is surgical replacement in the scrotum.	1b
The palpable testis is usually treated surgically using an inguinal approach.	2b
The non-palpable testis is most commonly approached laparoscopically.	2b
There is no consensus on the use of hormonal treatment for testicular descent.	2b

gestational age, affecting 1.0–4.6% of full-term and 1.1–45% of preterm neonates. Despite spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at 1 year of age [3]. This congenital malformation may affect both sides in up to 30% of cases [4]. In newborn cases with non-palpable or undescended testes on both sides and any sign of disorders of sex development (DSDs), such as concomitant hypospadias, urgent endocrinological and genetic evaluation is required [5].

Classification

The term cryptorchidism is most often used synonymously for undescended testes. The most useful classification of undescended testes is into palpable and non-palpable testes, and clinical management is decided by the location and presence of the testes (Fig. 1). Approximately 80% of all undescended testes are palpable [6]. Whether the condition is congenital or acquired can only be decided during a neonatal physical examination, documenting that the gonad is not in a proper scrotal position, compared with a testicle outside its normal position later in life, that was

Table 2 Recommendations.

	LE	GR
Do not offer medical or surgical treatment to boys with retractile testes but closely follow-up until puberty.	2a	A
Offer surgical orchidolysis and orchidopexy before the age of 12 months, and by 18 months at the latest.	2b	B
Evaluate male neonates with bilateral non-palpable testes for possible DSDs.	1b	A
In cases of non-palpable testes and no evidence of DSDs, offer laparoscopic intervention because of its excellent sensitivity and specificity in identifying an intra-abdominal testis, as well as the possibility for subsequent treatment in the same session.	1a	A
Do not routinely offer hormonal therapy, either in an adjuvant or neo-adjuvant setting for testicular descent. Patients have to be evaluated on an individual basis.	2a	C
In cases of bilateral undescended testes, offer endocrine treatment to possibly improve further fertility potential.	4	C
For an undescended testis in a post-pubertal boy or older, with a normal contralateral testis, discuss removal with the patient/parents because of the theoretical risk of a later malignancy.	3	B

documented as being scrotal after birth. Acquired undescended testes can be caused by entrapment after herniorrhaphy or spontaneously referred to as ascending testis.

Palpable testes include true undescended testes and ectopic testes. Non-palpable testes include intra-abdominal, inguinal, absent, and sometimes also some ectopic testes. Most importantly, the diagnosis of a palpable or non-palpable testis needs to be confirmed once the child is under general anaesthesia, as the first step of any surgical procedure for undescended testes.

Palpable testes

Undescended testes

A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on

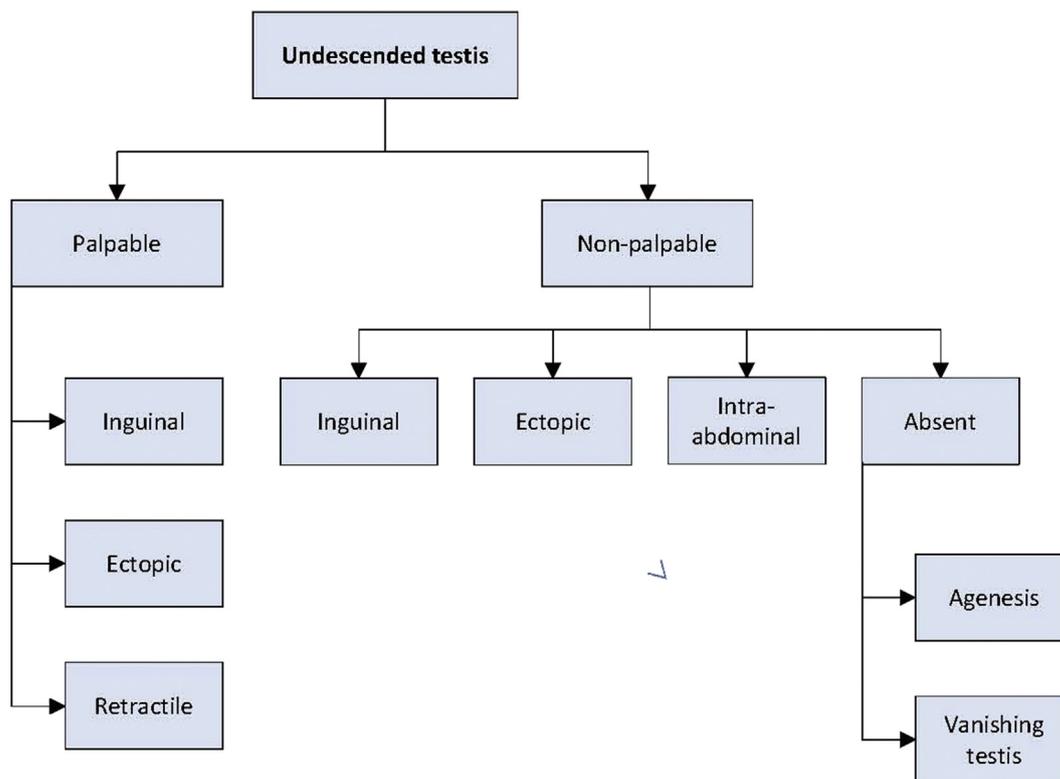


Figure 1 Classification of undescended testes.

the location, the testes may be palpable or not, as in the case of testes arrested in the inguinal canal.

Ectopic testes

If the position of a testis is outside its normal path of descent and outside the scrotum, the testis is considered to be ectopic. Although the most common aberrant position is in the superficial inguinal pouch, modern terminology used in many publications reserves the term ectopic testis for a testis that can be identified in a femoral, perineal, pubic, penile, or even contralateral position. Usually, there is no possibility for an ectopic testis to descend spontaneously to a correct position; therefore, it needs surgical intervention. Additionally, an ectopic testis may not be palpable because of its position.

Retractile testes

Retractile testes have completed their descent into a proper scrotal position but can be found again in a supra-scrotal position along the path of their normal descent. This results from an overactive cremasteric reflex [7]. Retractile testes can be easily manipulated down to the scrotum and remain there at least temporarily. They are typically normal in size and consistency. However, they may not be normal and should be monitored carefully as up to one-third can ascend and become undescended [8]. A study of 91 patients who were operated on and biopsied for ascending testes compared their histopathological findings to biopsies obtained from boys with primary undescended testes [9]. This study found that total germ cell count was not similar in the undescended and the contralateral descended testis in patients with ascending and primary

undescended testes, emphasizing the importance of following patients with retractile testes on an annual basis till after puberty.

Non-palpable testes

Among the 20% of non-palpable testes, 50–60% are intra-abdominal, canalicular, or peeping (right inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary.

Intra-abdominal testes

Intra-abdominal testes can be located in different positions, with most of them close to the internal inguinal ring. However, possible locations include the kidney, anterior abdominal wall, and retrovesical space. In the case of an open internal inguinal ring, the testis may be peeping into the inguinal canal.

Absent testes

Monorchidism can be identified in up to 4% of all boys with undescended testes, and anorchidism (bilateral absence) in <1%. Possible pathogenic mechanisms include testicular agenesis and atrophy after intrauterine torsion. Agenesis is thought to result from failed development of the testicular blood supply or from abnormal gonadal ridge differentiation, for example, in cases of complete 46XY gonadal dysgenesis. Atrophy indicates that, although the testicular vessels and vas deferens are found on surgical exploration, the testis itself is absent. The common hypothesis is *in utero* infarction of a normal testis by gonadal vessel

torsion. The term “vanishing testis” is commonly used for this condition [10].

Diagnostic evaluation

History taking and physical examination are key in evaluating boys with undescended testes. Localization studies using different imaging modalities are usually without any additional benefit.

History

Parents should be asked for maternal and paternal risk factors, including hormonal exposure, tobacco smoking, and genetic or hormonal disorders. If the child has a history of previously descended testes, this might be suggestive of testicular ascent [11]. Prior inguinal surgery is indicative of secondary undescended testes caused by entrapment.

Physical examination

Subsequent to a general physical examination and inspection of the corresponding region, an undescended testis is pursued by carefully advancing the examining fingers of warm hands along the inguinal canal towards the pubis region, perhaps with the help of lubricant. A possible inguinal testis can be felt to bounce under the fingers [12]. A non-palpable testis in the supine position may become palpable once the child is in a sitting or squatting position. If no testis can be identified along the normal path of descent, possible ectopic locations must be considered.

In case of unilateral non-palpable testis, the contralateral testis must be examined. Its size and location can have important prognostic implications. Any compensatory hypertrophy suggests testicular absence or atrophy [13]. Nevertheless, this does not preclude surgical exploration as the sign of compensatory hypertrophy is not specific [14].

In case of bilateral undescended testes and any evidence or sign of DSDs, such as uncertainty regarding the appearance of the external genitalia or scrotal hyperpigmentation, further evaluation including endocrinological and genetic assessment becomes mandatory [15]. This includes, among others, immediate karyotyping to rule out virilized cases of congenital adrenal hyperplasia as well as human chorionic gonadotrophin (hCG) testing to evaluate whether there is testicular tissue existing which reacts to stimulation and produces testosterone.

Imaging studies

Imaging studies cannot determine with certainty whether a testis is present or absent [16]. Although ultrasound is a non-invasive tool, it is time-consuming, costly, and in case of a non-palpable testis, lacks the diagnostic accuracy to detect confidently the presence of the testis or to establish the absence of an intra-abdominal testis [17].

Consequently, the use of different imaging modalities, such as ultrasound [18] or magnetic resonance imaging, for undescended testes is limited and only recommended in specific and selected clinical scenarios (e.g. identification

of Müllerian structures in cases with suspicion of DSDs) and determination of exact testicular size if needed [19].

Management

Treatment should be started at the age of 6 months, an undescended testis rarely descends after this age [20]. Any kind of treatment leading to a scrotally positioned testis should be finished by 12 months, or 18 months at the latest, as histological examination of undescended testes at 12–18 months has revealed a progressive loss of germ cells and Leydig cells [21]. The early timing of treatment is also driven by the final adult results on spermatogenesis and hormone production, as well as on the risk of tumour development [22].

Medical therapy

Unfortunately, most studies on hormonal treatment have been of poor quality, with heterogeneous and mixed patient populations, testis location, and schedules and dosages of hormonal administration. Additionally, long-term data are almost completely lacking.

Short-term side effects of hormonal treatment include increased scrotal erythema and pigmentation, and induction of pubic hair and penile growth. Some boys experience pain after intramuscular injection of hCG. All of these tend to regress after treatment cessation [23].

Medical therapy for testicular descent

Hormonal therapy using hCG or gonadotrophin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent, but has a maximum success rate of only 20% [24]. However, almost 20% of these descended testes have the risk of re-ascending [23]. In general, success rates depend on testicular location. The higher the testis is located prior to therapy, the lower the success rate, suggesting that testicular position is an important determinant of success [25]. Some authors recommend combined hCG–GnRH treatment. Unfortunately, this is poorly documented and the treatment groups were diverse. Some studies reported successful descent in up to 38% of non-responders to monotherapy [26]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE 4, GR C).

Human chorionic gonadotrophin stimulates endogenous testosterone production and is administered by intramuscular injection. Several dose and administration schedules have been reported. There is no proven difference between 1.5 IU and weight-based doses up to 3.0 IU every other day for 14 days [27]. Similar response rates were achieved with 500 IU once weekly and 1.5 IU three times weekly [28]. However, there is evidence that dosing frequency might affect testicular descent rates. Fewer lower dose injections per week for 5 weeks seem to be superior to one higher dose every 7–10 days for 3 weeks with regard to testicular descent [29].

Gonadotrophin-releasing hormone analogues (e.g. buserelin and gonadorelin) are available as nasal sprays, thus avoiding painful intramuscular injections. A typical dosage regimen consists of 1.2 mg/day in three divided

doses, for 4 weeks. Success rates are wide ranging, from 9% to 60%, most probably because of multiple treatment strategies and heterogeneous patient populations [30]. Additionally, in some European countries as well as in the USA GnRH analogues are not approved for use in children with undescended testis [31].

Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [32] and therefore serves as an additional tool to orchidopexy. There is benefit for treatment with GnRH before (neo-adjuvant) or after (adjuvant) surgical orchidolysis and orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life [33]. It is still unknown whether this effect on testicular histology persists into adulthood, but it has been shown that men who were treated in childhood with buserelin had better semen analyses compared with men who had childhood orchidopexy alone or placebo treatment [34].

It is only possible with the help of testicular biopsies during surgical orchidopexy in boys with undescended testes to predict future semen analyses and possibly identify patients at risk for testicular cancer. On the other hand, it has been suggested that testicular biopsies can be detrimental to the long-term health of the testis. However, in a study of 112 males who underwent fertility evaluation with a history of orchidopexy during childhood and testicular biopsy, the authors were able to demonstrate that not a single patient exhibited evidence of antisperm antibodies. In addition, they concluded that testicular biopsies did not increase the rate of testicular microlithiasis and they found no evidence of additive testicular damage associated with testicular biopsy at the time of orchidopexy [35]. Furthermore, in a follow-up paper of the same patients after 18 years of age, they were able to demonstrate no evidence of further loss of testes. The authors concluded that testis biopsy at orchidopexy may be limited in predicting future fertility in unilateral undescended testis, but more clinically useful in predicting fertility potential for those with bilateral undescended testes [36].

The possible additional risks of testicular biopsies such as bleeding, infection, even atrophy or loss of testis, and other parenchymal changes, must be taken into account, however, and weighed against the possible benefit to rule out which subtype of patients might benefit from additional hormonal treatment and which are at increased risk of testicular malignancy.

It has been reported that hCG or GnRH treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood [37].

Identification of specific subgroups of boys with undescended testes who would benefit from such an approach using hormones is difficult, as data on these specific groups as well as additional data on the long-term effects are still lacking. The Nordic consensus does not recommend hormonal therapy [38]. The Panel consensus recommends endocrine treatment with GnRH analogues in a dosage described above for boys with bilateral undescended testes to preserve their fertility potential (LE 4, GR C).

Surgical therapy

If a testis has not concluded its descent at the age of 6 months (corrected for gestational age), and as spontaneous testicular descent is unlikely to occur after that age, surgery should be performed within the subsequent year and by 18 months at the latest [21]. Early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [39]. All these findings recommend performing early orchidopexy between the ages of 6 and 18 months [20].

Palpable testes

Surgery for palpable testes includes orchidolysis and orchidopexy, either via an inguinal or scrotal approach. The latter approach is mainly reserved for low-positioned, undescended testes, with the pros and cons of each method being weighed against each other [40].

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [41]. Important inguinal orchidopexy steps include mobilization of the testis and spermatic cord to the level of the internal inguinal ring, with dissection and division of all cremasteric fibres, to prevent secondary retraction and detachment of the gubernaculum testis. The patent processus vaginalis needs to be ligated proximally at the level of the internal ring, because an unidentified or inadequately repaired patent processus vaginalis is an important factor leading to failure of orchidopexy [42]. Any additional pathology must be dealt with, such as removal of an appendix testis (hydatid of Morgagni). At this time the size of the testis can be measured and the connection of the epididymis to the testis can be judged and described in the protocol. Some boys have a significant dissociation between testis and epididymis which is prognostically bad for fertility. Finally, the mobilized testicle must be placed in a sub-dartos pouch within the hemi-scrotum without any tension. In case the length achieved using the above-mentioned technique is still inadequate, the Prentiss manoeuvre, which consists of dividing the inferior epigastric vessels and transposing the spermatic cord medially, to provide a straight course to the scrotum, might be an option [43]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [44]. Lymph drainage of a testis that has undergone surgery for orchidopexy may have changed from high retroperitoneal drainage to iliac and inguinal drainage, which might become important in the event of later malignancy [45].

Low-positioned, palpable undescended testis can be fixed through a scrotal incision including division of the gubernaculum, and the processus vaginalis needs to be probed to check for patency [46]. Otherwise, fixation in the scrotum is carried out correspondingly to the inguinal approach. In up to 20% of cases, an inguinal incision will be compulsory to correct an associated inguinal hernia [47]. Any testicular or epididymal appendages can be easily identified and removed. A systematic review showed that overall success rates ranged from 88% to 100%, with rates of recurrence and postoperative testicular atrophy or hypotrophy of <1% [40].

Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [48]. If a testis is found, the decision has to be made to remove it or bring it down to the scrotum. An important step in surgery is a thorough re-examination once the boy is under general anaesthesia, as a previously non-palpable testis might be identifiable and subsequently change the surgical approach to standard inguinal orchidopexy, as described above (Fig. 2). Otherwise, the easiest and most accurate way to locate an intra-abdominal testis is diagnostic laparoscopy [49]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [50]. Some surgeons tend to start with inguinal exploration, with possible laparoscopy during the procedure [51]. In case an ipsilateral scrotal nubbin is suspected, and contralateral compensatory testicular hypertrophy is present, a scrotal incision with removal of the nubbin, thus confirming the vanishing testis, is an option removing the need for laparoscopy [52].

During laparoscopy for non-palpable testes, possible anatomical findings include spermatic vessels entering the inguinal canal (40%), an intra-abdominal (40%) or peeping (10%) testis, or blind-ending spermatic vessels confirming vanishing testis (10%) [53].

In case of a vanishing testis, the procedure is finished once blind-ending spermatic vessels are clearly identified. If the vessels enter the inguinal canal, one may find an atrophic testis on inguinal exploration or a healthy testis that needs to undergo standard orchidopexy [54]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [55]. Placement of an intra-abdominal testis can sometimes be a surgical challenge. Usually, testes lying >2 cm above the internal inguinal ring may not reach the scrotum without division of the testicular vessels [56]. Under such circumstances, a Fowler–Stephens orchidopexy might be an option [1].

Proximal cutting and transection of the testicular vessels, with conservation of the collateral arterial blood supply, via the deferential artery and cremasteric vessels,

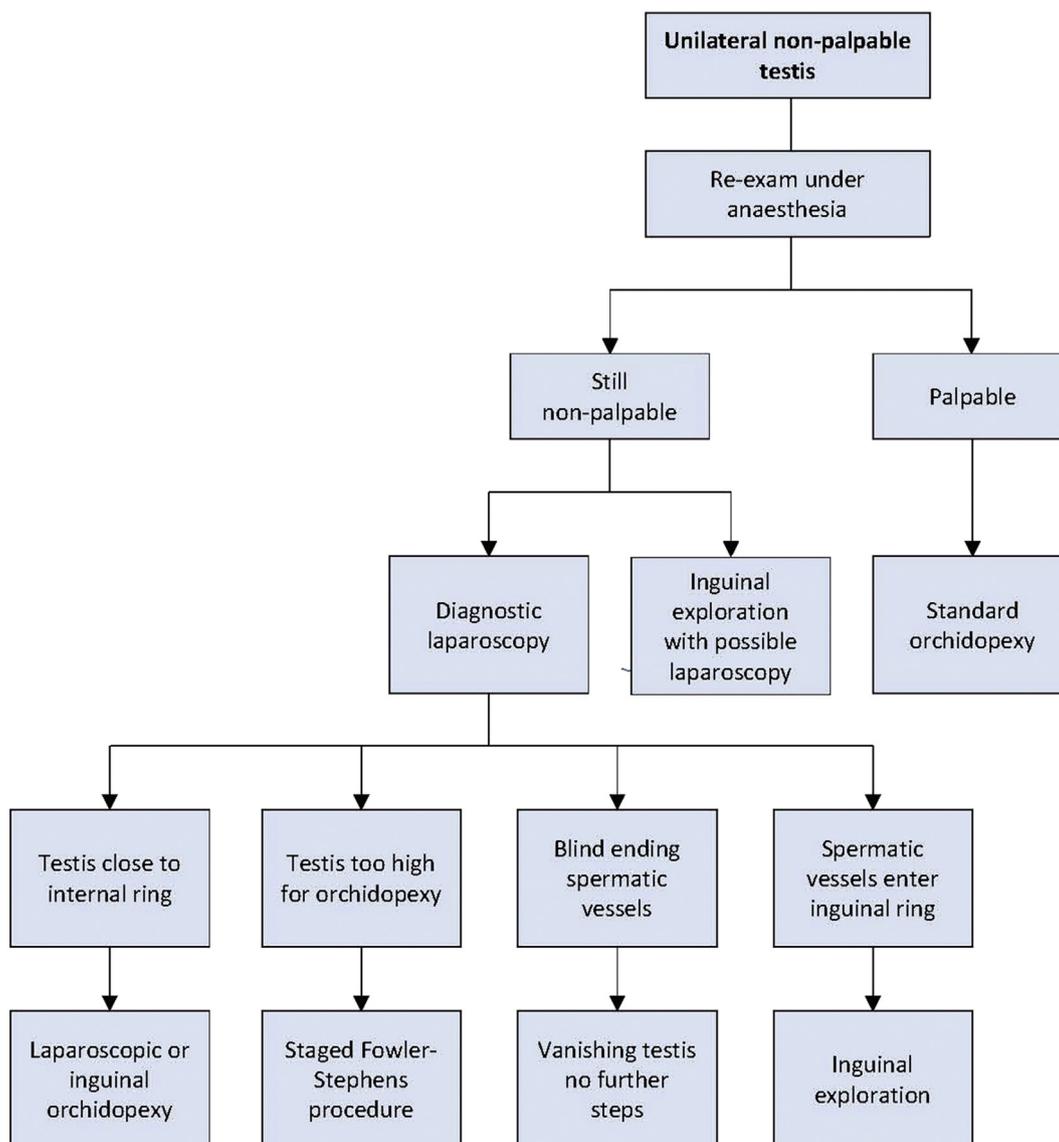


Figure 2 Algorithm for unilateral non-palpable undescended testis.

comprise the key features of the Fowler–Stephens procedure. Recently, a modification with low spermatic vessel ligation has gained popularity, allowing blood supply from the testicular artery to the deferential artery. An additional advantage is the position of the peritoneal incision, leading to a longer structure, to ease later scrotal placement [57]. It is within the nature of these approaches that the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [58]. The testicular survival rate in the one-stage Fowler–Stephens technique varies between 50% and 60%, with success rates increasing to up to 90% for the two-stage procedure [59], although some other studies are suggestive of lower success rates. The advantages of two-stage orchidopexy, with the second part done usually 6 months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [60]. In addition, preservation of the gubernaculum may also decrease the chance of testicular atrophy [61].

An alternative might be microsurgical auto-transplantation, which has a success rate of up to 90%. However, this approach requires skilled and experienced surgeons and is performed in only a few centres [62]. That experience is limited and the numbers of patients published are very low.

Complications of surgical therapy

Surgical complications are usually uncommon, with testicular atrophy being the most serious. This phenomenon is typically a result of injury to the spermatic vessels during surgery, tension on the cord, with subsequent ischaemia, iatrogenic torsion, and intentional ligations of the vessels as an integral part of Fowler–Stephens orchidopexy. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler–Stephens procedure, and 8.2% for the two-stage approach [63].

Other rare complications comprise testicular ascent and vas deferens injury besides local wound infection, dehiscence, and haematoma.

Surgical therapy for undescended testes after puberty

A recent study on 51 men diagnosed with an inguinal unilateral undescended testis and a normal contralateral one, with no history of any previous therapy, demonstrated a wide range of changes on histological evaluation. Half of the study population still had significant germ cell activity at different maturation levels. Importantly, the incidence of intratubular germ cell neoplasia was 2% [64].

The Panel consensus recommends offering the possibility of orchiectomy in post-pubertal boys with an undescended testis and a normal contralateral one in a scrotal position.

Undescended testes and fertility

The association of undescended testes with compromised fertility [65] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [66], Leydig cell diminution, and testicular fibrosis [67].

Although boys with one undescended testis have a lower fertility rate, they have a similar paternity rate to those with bilateral descended testes. Boys with bilateral undescended testes suffer both lower fertility and paternity rates. Fertility rate is the number of offspring born per mating pair, individual of population, whereas paternity reflects the actual potential of fatherhood [68].

The age at which surgical intervention for an undescended testis happens seems to be an important predictive factor for fertility later in life. Endocrinological studies revealed higher inhibin-B and lower follicle-stimulating hormone (FSH) levels in men who underwent orchidopexy at age 2 years compared with individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [69]. These studies were able to demonstrate that age at orchiopexy significantly correlated with hormone levels such as inhibin-B and FSH as well as sperm density. For these studies, the population was divided into four different age groups (0–2, 2–5, 5–8, and 8–11 years) with the best results for fertility outcome in the group aged 0–2 years [69]. In addition, other studies have demonstrated a relationship between undescended testes and increased loss of germ cells and Leydig cells, which is also suggestive of prompt orchidopexy being a significant factor for fertility preservation [70].

Outcome studies for untreated bilateral undescended testes revealed that 100% are oligospermic and 75% azoospermic. Among those successfully treated for bilateral undescended testes, 75% still remain oligospermic and 42% azoospermic [67].

In summary, regarding preservation of fertility potential, early surgical correction of undescended testes is highly recommended before 12 months of age, and by 18 months at the latest [21].

Undescended testes and malignancy

Boys who are treated for an undescended testis have an increased risk of developing testicular malignancy. Screening and self-examination both during and after puberty is therefore recommended [71].

A Swedish study, with a cohort of almost 17,000 men (56 developed a testicular tumour) who were treated surgically for undescended testes and followed for ~210,000 person-years, showed that management of undescended testes before the onset of puberty decreased the risk of testicular cancer [72]. The relative risk of testicular cancer among those who underwent orchidopexy before 13 years of age was 2.2 compared with the Swedish general population; this increased to 5.4 for those treated after 13 years of age.

A systematic review and meta-analysis of the literature also concluded that pre-pubertal orchidopexy may reduce the risk of testicular cancer and that early surgical intervention is indicated in boys with undescended testes [73].

Follow-up

Apart from the routine follow-up of patients regarding postoperative complications and ensuring the viability and correct position of the testis after orchidopexy, there are two important additional parameters which correlate with

the problem of undescended testis: impairment of fertility and potential risk of malignancy. Counselling and educating parents and patients regarding these possible long-term effects is essential. It is recommended that a patient with a history of undescended testis is instructed to perform a proper monthly self-exam of the testes.

In cases of testicular atrophy the patient can be offered a testicular prosthesis taking into account the risks of infection and migration of the prosthesis, which may lead to subsequent removal of the implant.

Conflict of interest

None.

Funding

None.

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