REVIEW ARTICLE

The Undescended Testis: Diagnosis, Treatment and Long-Term Consequences

Michael J. Mathers, Herbert Sperling, Herbert Rübber, Stephan Roth

SUMMARY

Background: The late descent of a testicle into the scrotum may impair its development. Reduced fertility is the main risk of primary cryptorchidism even after timely treatment, as histopathological changes (Leydig cell hypoplasia) already become apparent in the first few months of life. There is evidence, however, that treatment is often delayed. Hormonal and surgical treatments complement each other and should be provided before the child's first birthday.

Methods: Selective literature search in PubMed (January 2008) based on the following keywords: „cryptorchidism“, „maldescensus testis“, „etiology“, „therapy“, „semen quality“, „testicular cancer“. Particular attention was paid to the current S2 guidelines on cryptorchidism.

Results/Discussion: Hormone therapy is the best initial treatment in most cases, with a few exceptions. If this is unsuccessful, surgery should be performed without delay. The success of treatment depends on the initial position of the testicle. Treatment does not lessen the risk of malignancy. Parents must be informed about this risk. The undescended testicle is the most common genital malformation in boys. When diagnosed, it should be treated hormonally and/or surgically before the child's first birthday to minimize the risk of impaired fertility. Successful treatment before age 13 appears not to lessen the risk of testicular cancer, but it does facilitate early detection by enabling physical examination of the testicle.

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Key words: Maldescensus testis, cryptorchidism, fertility, hormonal treatment, surgical treatment, malignancy

Undescended testis is the commonest genital malformation in boys. Although the mechanism that regulates prenatal testicular descent is still partly obscure, there is persuasive evidence that endocrine, genetic, and environmental factors are involved (1, e1).

The treatment of undescended testis should begin after six months and ideally be completed by the child's first birthday (2). In Germany, there is a general consensus about the need to raise awareness of the importance of timely management of undescended testis (3). Treatment comprises hormonal and/or surgical approaches. Men with untreated bilateral cryptorchidism suffer from impaired fertility (e2). Early treatment can potentially minimize the risk of infertility, although treatment before the age of 13 doesn't appear to lessen the risk of malignancy (4). Scrotal positioning, however, allows easier examination of the testicle—usually by self-examination—which favors early detection of malignancy (5, e3). The current S2 guidelines describe in detail a diligent follow up for up to one year postoperatively (2). For adults, there is no consensus recommendation although it is known that undescended testis, even if successfully treated, may have long-term consequences for testicular function and the development of testicular cancer. The latter applies especially to boys in whom treatment is delayed (4).

Purpose and method of the review article

This article provides an overview of the diagnosis and treatment of undescended testis and gives special consideration to the long-term consequences. The literature search was performed in January 2008 in PubMed without a retrospective time limit and using the following key words: "cryptorchidism", "maldescensus testis", "aetiology", "semen quality", and "testicular cancer".

Systematic reviews and, where available, meta-analyses of randomized, controlled studies were identified and then linked to the content-related criteria. The current S2 guideline of January 2008 for undescended testis issued by the German Society of Pediatric Surgery, the German Society for Urology, and the German Society of Pediatric and Adolescent Medicine were taken particularly into account.

Prevalence

Up to one third of premature boys are affected by maldescensus testis, while about 2% to 5% of full-term boys have at least one undescended testicle (6). Short-term

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BOX

Different forms of undescended testis

Undescended testis can be categorized on the basis of physical examinations (modified from [20]):

- Undescended testis The testicle is located intra-abdominally or in the inguinal canal. It is located in the normal descent pathway and shows normal insertion of the gubernaculum.
- Cryptorchidism From the ancient Greek "kryptos" (hidden) and "orchis" (testicle). The testicle is not palpable and is located intra-abdominally (retentio testis abdominalis) or is not present (anorchia).
- Ektopia testis The testicle is located beneath the skin superfascially, perineally, on the thigh or shaft of the penis. The testicle shows abnormal insertion of the gubernaculum.
- Inguinal testicle The testicle is palpable in the groin (retentio testis inguinalis)
- Gliding testicle The testicle is located at the scrotal entrance or above the scrotum. It can be drawn down into the scrotum, but immediately slides back into its initial position.
- Retractable (hypermobile) testes The physiological retractile (hypermobile) testicle is usually present in the scrotum or can be effortlessly pushed down into the scrotum, it retracts on induction of the cremasteric reflex but returns spontaneously into the scrotum. Recognizing the retractile (hypermobile) testicle is particularly important because it does not require treatment.

postnatal endogenous testosterone secretion reduces this incidence to 1% to 2% after three months (6). A strategy of watchful waiting is no longer indicated after six months according to the literature, since in these cases spontaneous descent occurs only very rarely (5, 7).

The physiological process of testicular descent is hardly elucidated. Similarly, the exact causes of maldevelopment are unknown.

A birth weight below 2.5 kg and premature delivery are risk factors for maldevelopment. Placental insufficiency with reduced human chorionic gonadotropin (hCG) secretion (e4) appear to play an equally significant role as a reduced maternal estrogen level (e5).

Evidence is mounting that environmental factors increase the risk of cryptorchidism. Persistent organochlorine compounds, mono-esters of the phthalates, maternal smoking, and maternal diabetes mellitus are also risk factors for maldevelopment of the male reproductive organs (e6, e7, 8).

Many undescended testicles are accompanied by patency of the vaginal process (e8). This, like the simultaneous presence of inguinal hernia, is treated surgically during the orchidofuniculolysis procedure.

Examination and diagnosis

Testicular examination in infants and young children requires experience and should always be performed using a two-handed technique. Palpation should take place in anxiety-free and warm surroundings, since cold or anxiety can cause the cremasteric reflex to retract the testicle. One hand strokes from the upper iliac spine along the inguinal canal towards the pubic bone, while the other hand attempts to palpate the testicle. With this maneuver it is frequently also possible to push the testicle towards the scrotum, causing it to become positioned at the outer inguinal ring. When the testicle is released, it immediately jumps from the upper scrotal compartment towards the inguinal canal (gliding testicle). In contrast, the retractile (hypermobile) testicle remains in the scrotum until the cremasteric reflex is triggered and only then does the testicle disappear in cranial direction (Box).

As an imaging technique, sonography with a high-resolution transducer (>7.5 MHz) provides a correct classification rate (accuracy) of 84% for non-palpable testicle (with a sensitivity of 76% and a specificity of 100%) (Figure 1) (e9). This initial identification of the inguinal testicle allows an assessment in terms of size and parenchymal structure. In the search for an intra-abdominal testicle, MRI can be expected to provide a correct classification (accuracy) of 85% with a sensitivity of 86% and a specificity of 79% (e9). The method now preferred for the localization of non-palpable testicle is laparoscopy (2).

There is generally no need for diagnostic laboratory tests. For a male newborn with bilateral non-palpable testicle, a female karyotype with accompanying adrenogenital syndrome must be ruled out. For bilateral non-palpable testicles, a pediatric endocrinological assessment is indicated, among other things in order to rule out other syndromes. Detection of testosterone-producing testicular tissue should precede surgical exploration and can be accomplished with the conventional hCG stimulation test (Figure 2).

Increases in luteinizing hormone (LH), follicle-stimulating hormone (FSH) and the non-measurability of Mullerian inhibiting substance (MIS) are suggestive of anorchia (e10). Elevated gonadotropins and a negative intramuscular human chorionic gonadotropin (hCG) stimulation test (Figure 2) without evidence of testosterone production reinforce this assumption. Final proof of anorchia, however, is provided by surgical exploration.

Treatment of cryptorchidism

The treatment of cryptorchidism is hormonal, surgical, or a combination of both. The success of treatment depends on the position of the testicle at diagnosis. The use of human chorionic gonadotropin (hCG) stimulates the Leydig cells of the testicle to produce testosterone. Gonadotropin releasing hormone (GnRH) stimulates the pituitary to secrete luteinizing hormone (LH) which in turn stimulates the Leydig cells of the testicle to produce testosterone and thereby initiate descent.

Orchidopexy is the standard operation for undescended testis (e11). It should primarily be performed for testicular ectopy, simultaneous inguinal hernia, after previous inguinal surgery, for relapses, in older infants, or after unsuccessful hormone therapy. For the non-palpable testicle, the open operation/laparoscopy is simultaneously diagnostic and therapeutic.

Treatment time schedule

New findings suggest it is preferable to await spontaneous descent during the first six months. In the event of non-descent, preoperative combined hormone therapy should be initiated especially with a view to improving subsequent fertility. If this is unsuccessful, surgery is indicated. The treatment, including the surgical correction, should be completed by the child's first birthday (2). Since re-ascension occurs in about 24% of boys after hormone therapy (e12), it is advisable to monitor these boys for at least six months (2). If cryptorchidism requiring treatment is discovered after the first birthday, surgical intervention should be the primary approach.

Hormone therapy

In the new guidelines (2), two goals of hormone therapy are pursued:

- induction of descent of the retained testicle and
- stimulation of germ cell maturation and proliferation to contribute to improving fertility.

The prospects of success of hCG therapy reported in the literature vary between 20% and 99% in controlled studies (e13, e14, 10), with most studies achieving a hormone therapy success rate of around 20% (e15, e16) or even less, when retractile (hypermobile) testicles—which do not require treatment—are explicitly excluded (e17). The cause of these discrepancies lies in the many different dosages, treatment intervals, and age differences of the treated boys.

Side effects of hCG therapy may include enlargement of the penis (3%), growth of genital hair, testicular enlargement, and aggressive behaviour of the child during the treatment (1%) (e18). Success rates of GnRH therapy also vary greatly in controlled studies (0% to 78%). In a comparative randomized double-blind study, clinical success was observed in 6% of the boys treated with hCG and in 19% after GnRH treatment (10). In a meta-analysis of 33 randomized studies in 3282 boys with 4524 undescended testicles, the success rate was 19% with hCG, 21% with GnRH, and 4% with placebo (e16).

In a prospective randomized study, neoadjuvant GnRH therapy improved the fertility index (number of adult dark spermatogonia per tubule) (e15). According to the above guideline (2), LHRH therapy should be initiated (Table).

Regardless of the outcome, hCG is administered immediately afterwards. This combination can be expected to induce descent in around 20% of cases (e16). Whether this can simultaneously improve the maturation of the germinal epithelium accompanied by an improve-

The different testicle locations in cryptorchidism

ment of fertility in adulthood is uncertain. To what extent hCG also has negative effects has not yet been conclusively established (11, e15, e19).

Postoperative hormone therapy

Postoperative hormone therapy with low dose GnRH analogs appears to provide benefits for later fertility (e19, 12). The current literature does not justify a routine use of postoperative hormone therapy. This approach should be individualized and be discussed with the parents.

Testicular biopsy

As a means of determining the maturation status of the testicle, intraoperative testicular biopsy is controversial and at present reserved for use in studies. It is however indicated if ovotestis (the simultaneous presence of testicular and ovarian tissue in one germ cell), dysgenesis, or tumor is suspected.

Surgical treatment

The purpose of the operation is to search for the retracted testicle and, after adequate orchidolysis, to achieve tension-free transfer to and fixation in the scrotum. For intra-abdominal testicle, this is possible using either an open surgical or laparoscopic technique. The two methods can be regarded as equivalent. Since in about 5% of cases the operation cannot be completed with the chosen technique (e20, e21), it should be possible to switch to the other technique during the procedure.

FIGURE 2

hCG stimulation test

The hCG stimulation test is used to demonstrate the presence of functional testicular tissue. It is therefore only useful in bilateral cryptorchidism. Stimulated testosterone values are compared before and 32 hours after an intramuscular dose of 5000 IU hCG. If functional testicular tissue is present, the testosterone values increase to twice the baseline value after hCG administration. Increased baseline FSH and LH values associated with an absent testosterone increase after stimulation demonstrates the absence of functional testicular tissue. With a normal phenotype and normal 46-XY karyotype, the diagnosis anorchia can be regarded as certain (modified from [9]).

TABLE

Treatment schedule for undescended testis

Medication	Dosage
LHRH (luteinizing hormone releasing hormone)	3 x 400 µg / d (i.e. 3 x daily one puff of 200 µg into each nostril) over 4 weeks as nasal spray
immediately followed by human chorionic gonadotropin (hCG)	500 IU intramuscular injection at weekly interval for three weeks

*modified from 2

If this treatment fails, open surgical orchidolysis and orchidopexy or laparoscopic techniques are employed. Treatment should begin after six months and be completed by the child's first birthday.

Testicular aplasia is diagnosed in 9.8% of boys with intra-abdominal testicle (13). In some cases only rudiments are found at the end of the spermatic cord and these should then be removed.

A meta-analysis of 64 studies in 8425 cryptorchid testicles reported the following success rates:

- for testicles that were originally distal to the outer inguinal ring, 92%
- for "true" inguinal testicle, 87%
- for intra-abdominal testicle, 74% (evidence level III) (14)
- for laparoscopic orchidopexies of intra-abdominal testicles, the success rates are above 90% (15, e22).

In the "laparoscopic testicle search" for intra-abdominal testicle, ligation of the testicular vessels (Fowler-Stephens maneuver) is an easy-to-perform technique of extending the diagnostic to the surgical procedure (16, 17, e23).

The synonym "Fowler-Stephens operation" describes the surgery of the intra-abdominal testicle by intraperitoneal ligation of the testicular vessels while reliably sparing the vessels of the ductus deferens (evidence level IV) (18).

A distinction is made between the single-stage and two-stage Fowler-Stephens orchidopexy, although the single-stage variant is now hardly used as it leaves no time for the formation of further collateral circulations. A meta-analysis by Docimo for the Fowler-Stephens two-stage operation reported 77% prospects of success (evidence level III) (14, 15).

Autotransplantation, in which the testicular vessels are anastomosed with vessels of the intra-abdominal wall, is limited mainly by the decreasing vascular diameter at early operative age despite the use of microsurgical techniques. A meta-analysis found a success rate of 84% (evidence level III [14], evidence level IV [19]).

One complication of orchidopexy is testicular atrophy. Division of the testicular vessels and/or postoperative swellings and infections can result in testicular ischemia and cause (partial) atrophy of the testicle. Although this is a rare complication, the meta-analysis of the available literature shows that even relatively distal testicles have a failure rate of up to 8%. For intra-abdominal testicles, this figure is more than 25%. Other complications besides infections and secondary hemorrhage are relapses necessitating repeat surgery. A repeat intervention should not be scheduled earlier than six months after the first operation.

Whether a testicular rudiment (atrophic testicle, non-growing testicle) can be left in situ is uncertain. In most cases removal is recommended to eliminate in advance the possibility of subsequent malignant degeneration when residual testicular tissue is present. This alternative should be discussed with the parents before the operation.

Infertility

Men with a history of undescended testis have a reduced probability of fertility with a low sperm count and generally poorer semen quality than men with normal testicular descent (e24, 20). This subfertility is not compensated by a normally descended contralateral testis. The probability of a fertility impairment is additionally increased in bilateral cryptorchidism and delayed treatment of the non-descended testicle. Almost all adult men with bilateral undescended testis have azoospermia, whereas more than 20% of boys achieve a normal sperm count after orchidopexy. Only few studies have evaluated semen quality in relation to the time of life at which treatment was performed, the original position of the testicle, and the surgical technique. Surgical treatments in boys between the ages of ten months and four years with bilateral cryptorchidism

lead to a normal sperm count in 76% of cases compared to 26% in the boys who were operated between the age of 4 and 14 years (21). This time effect is not so pronounced with unilateral cryptorchidism (21). This may well be due to the impaired spermatogenesis which is already characterized histologically in the first months of life by an increasing reduction in the testosterone-producing Leydig cells, delayed onset of spermatogonia, and a quantitatively and qualitatively reduced maturation process of the germ cells (e25). It is found that fertility may still be impaired after treatment and that early management confers distinct benefits (e24, 22).

Malignancy

It is now well documented that men with a history of cryptorchidism have a higher likelihood of developing a testicular germ cell tumor. The probability is 1 : 2000 (e26) and is increased 32 fold compared to the general population (3). A meta-analysis of 21 controlled studies showed an increased odds ratio of 3.5 to 17.1 in men with a history of undescended testis (23). The risk is highest with intra-abdominal testicle, five times higher than for inguinal cryptorchidism. The etiology of testicular malignancy is unknown, but epidemiological studies indicate a relationship between intrauterine and perinatal testicular development and undescended testis (e27, e28). The consensus view is that the mechanism that leads to cryptorchidism is already set in motion before birth or in infancy (24, 25).

Testicular malignancies develop from pre-invasive lesions, carcinoma in situ (CIS) or TIN (testicular intraepithelial neoplasia) (e29). In a study in 300 men with previous orchidopexy, subsequent testicular biopsy revealed a TIN in 1.7% (e28). Routine testicular biopsy at the time of orchidopexy in childhood is not recommended. The risk of developing testicular malignancy is higher with bilateral than with unilateral undescended testis. In men with unilateral cryptorchidism, in the majority of cases the malignancy is on the affected side, although malignant degeneration is found on the descended side in about 20% of cases (e30). Whether the surgical correction before puberty has an influence on the risk of malignancy is a contentious issue (5, e31). The results, obtained in a cohort of 16 983 patients, show that the risk of malignancy is almost twice as high in boys not operated until after age 13 years (4). A testicular tumor can definitely be detected more easily when self-examination is made easier (3).

Conclusion

The undescended testis is the most common genital malformation in boys and should be treated before the child's first birthday. If medicinal therapy (LHRH and hCG) is ineffective, orchidopexy should be performed immediately to reduce the risk of further damage to the testicular tissue. The boy's parents must be informed that correcting the cryptorchidism will facilitate future examination of the testicle, but will not reduce the risk of malignancy.

Key messages

- After the third month of life the incidence is around 1%.
- After the sixth month of life spontaneous descent is rare.
- Correction of testicular position should be done at the latest by the child's first birthday.
- Hormonal and surgical treatment are complementary modalities.
- Parents should be informed of the possibility of testicular malignancy and reduced prospects of fertility.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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