Evaluation and Treatment of Cryptorchidism: AUA Guideline

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Purpose: Cryptorchidism is one of the most common pediatric disorders of the male endocrine glands and the most common genital disorder identified at birth. This guideline is intended to provide physicians and non-physician providers (primary care and specialists) with a consensus of principles and treatment plans for the management of cryptorchidism (typically isolated non-syndromic).

Materials and Methods: A systematic review and meta-analysis of the published literature was conducted using controlled vocabulary supplemented with key words relating to the relevant concepts of cryptorchidism. The search strategy was developed and executed by reference librarians and methodologists to create an evidence report limited to English-language, published peer-reviewed literature. This review yielded 704 articles published from 1980 through 2013 that were used to form a majority of the guideline statements. Clinical Principles and Expert Opinions were used for guideline statements lacking sufficient evidence-based data.

Results: Guideline statements were created to inform clinicians on the proper methods of history-taking, physical exam, and evaluation of the boy with cryptorchidism, as well as the various hormonal and surgical treatment options.

Conclusions: Imaging for cryptorchidism is not recommended prior to referral, which should occur by 6 months of age. Orchidopexy (orchiopexy is the preferred term) is the most successful therapy to relocate the testis into the scrotum, while hormonal therapy is not recommended. Successful scrotal repositioning of the testis may reduce but does not prevent the potential long-term issues of infertility and testis cancer. Appropriate counseling and follow-up of the patient is essential.

Key Words: cryptorchidism, undescended testis, hormone, infertility, testis cancer

Abbreviations and Acronyms

AHRQ = Agency for Healthcare Research and Quality
CT = computerized tomography
DSD = disorder of sex development
FDA = Food and Drug Administration
FS = Fowler-Stephens
FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
hCG = human choronic gonadotropin
LH = luteinizing hormone
LHRH = luteinizing hormone-releasing hormone
MIS = müllerian inhibiting substance
MRI = magnetic resonance imaging
UDT = undescended testis
US = ultrasound

The complete guideline is available at http://www.auanet.org/education/guidelines/cryptorchidism.cfm.

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Cryptorchidism or undescended testis is one of the most common pediatric disorders of the male endocrine glands and the most common genital disorder identified at birth. Cryptorchidism is defined as failure of a testis to descend into a scrotal position. This situation most commonly refers to a testis that is present but in an extrascrotal position, but may also lead to identification of an absent testis. In the latter situation, the testis is most commonly referred to as vanishing (or vanished); consistent with evidence suggesting that it was present initially but disappeared during development most likely due to spermatic cord torsion or vascular

0022-5347/14/1922-0337/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.05.005
Vol. 192, 337-345, August 2014
Printed in U.S.A.

accident. The main reasons for treatment of cryptorchidism include increased risks of impairment of fertility potential, testicular malignancy, torsion and/or associated inguinal hernia. The current standard of therapy in the United States is orchidopexy (orchiopexy is the preferred term), or surgical repositioning of the testis within the scrotal sac, while hormonal therapy has fewer advocates. Successful scrotal relocation of the testis, however, may reduce but does not prevent these potential long-term sequelae in susceptible individuals. The purpose of this guideline is to provide physicians and non-physician providers (primary care and specialists) with a consensus of principles and treatment plans for the management of cryptorchidism (typically isolated nonsyndromic; intensive discussion of disorders of sex development is beyond the scope of this guideline). The panel members are representative of various medical specialties (pediatric urology, pediatric endocrinology, general pediatrics).

METHODOLOGY

The primary source of evidence for this guideline was the systematic review conducted as part of the Agency for Healthcare Research and Quality Comparative Effectiveness Review titled *Evaluation and Treatment of Cryptorchidism (2012)*. That report included systematic searches of MEDLINE®, Cumulative Index to Nursing and Allied Health Literature, and EMBASE® for English-language studies published from January 1980 through February 2012 relevant to cryptorchidism. To capture more recently published manuscripts to augment and broaden the body of evidence provided in the original AHRQ report, the American Urological Association conducted additional supplementary searches of PubMed® and EMBASE for relevant articles published between January 1980 and March 2013 that were systematically reviewed using a methodology developed *a priori*. In total, these searches yielded 704 studies, after exclusions, that were used to inform the statements presented in the guideline as Standards, Recommendations or Options and the accompanying treatment algorithm (see figure). When sufficient evidence existed, the body of evidence for a particular clinical action was assigned a strength rating of A (high), B (moderate) or C (low). In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens. For a complete discussion of the methodology and evidence grading, please refer to the unabridged guideline available at http://www.auanet.org/education/guidelines/cryptorchidism.cfm.

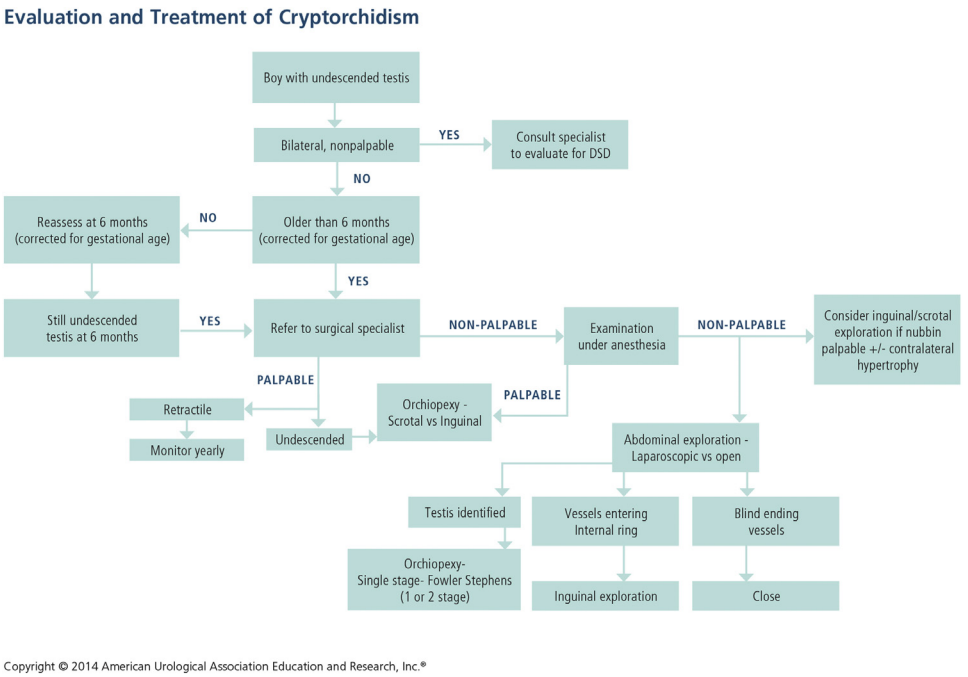

Figure.

GUIDELINE STATEMENTS

Diagnosis

1. Providers should obtain gestational history at initial evaluation of boys with suspected cryptorchidism. (*Standard; Evidence Strength: Grade B*)

Testicular descent occurs in two phases: transabdominal descent and inguinoscrotal migration. Initial transabdominal descent occurs in the first trimester of gestation. At approximately 22–25 weeks of gestational age, the testes are located at the internal ring. The inguinoscrotal phase of testicular descent, which is androgen dependent, occurs between 25–30 weeks.[1,2] Given the relatively late migration of testes through the inguinal canal into the scrotum, the prevalence of cryptorchidism is higher in premature boys in the first months of life (1–3% in full-term and 15–30% in premature male infants).[3] Descent of the testes into the scrotum is probable in premature boys during the first months of life, but is unlikely after six months of corrected age.[4,5] Obtaining the gestational age is thus critical to the proper and timely referral of a child with persistent undescended testes to a surgical specialist.

In addition to gestational age, low birth weight for gestational age has also been closely associated with cryptorchidism: the prevalence of cryptorchidism in infants <900g is approximately 100%. The prevalence of cryptorchidism decreases as the birth weight of the infant increases, and is approximately 3% in infants weighing 2,700–3,600 g.[3,6] Spontaneous postnatal testicular descent may be lower in boys with cryptorchidism and a history of small-for-gestational age compared to boys with cryptorchidism and normal birth weight.[4,6]

2. Primary care providers should palpate testes for quality and position at each recommended well-child visit. (*Standard; Evidence Strength: Grade B*)

A UDT may be located in the abdomen, the inguinal canal, the superficial inguinal pouch, the upper scrotum, or, may rarely be in an ectopic location (perineum, contralateral scrotum, or femoral). Approximately 70% of UDTs are palpable.[7] For testes that are not palpable, approximately 30% will be found in the inguinal-scrotal area, 55% will be intra-abdominal, and 15% will be absent or vanishing.[8] Testicular position may change as infants and children grow.

Spontaneous descent of testes may occur in the first six months of life.[4,5] Additionally, testes may "ascend" out of the scrotum (acquired cryptorchidism). Given the potential for change in testicular position throughout childhood, careful evaluation of the scrotum should be performed at every scheduled well-child check.

A genital examination should be performed at every well-child check as outlined by the Bright Futures of the American Academy of Pediatrics.[9] Documentation of testes in the dependent scrotum in the first few years of life should not preclude continued examination of the genitals at every scheduled clinic visit. Systematic genital examination will allow identification and referral of boys with acquired cryptorchidism (see Guideline Statement 4). Acquired cryptorchid testes are at risk for developing the same adverse histologic changes seen in primary cryptorchid testes and contribute to the number of orchiopexies performed.[10] Continued genital examinations will also allow identification of boys with retractile testes. While retractile testes do not require surgical correction, the risk of testicular ascent may be higher in boys with retractile testes than in boys whose testes are always positioned in the dependent scrotum.[11] Therefore, children with retractile testes should be monitored for "ascent" of the affected testis.

3. Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by six months (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (*Standard; Evidence Strength: Grade B*)

Testes that remain undescended by six months (corrected for gestational age) are unlikely to descend spontaneously.[4] In order to facilitate timely orchidopexy, boys whose testicle(s) remain undescended by six months (corrected for gestational age) should be referred to an appropriate surgical specialist.[12] The rationale for referral by six months (corrected for gestational age) is the low probability of spontaneous descent and the probable continued damage to testes that remain in a non-scrotal location.

4. Providers should refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after six months (corrected for gestational age) to an appropriate surgical specialist. (*Standard; Evidence Strength: Grade B*)

Acquired cryptorchidism is the ascent of a previously descended testis and subsequent inability to manipulate the testis back into the scrotum. Acquired cryptorchidism is a clinical condition distinct from primary UDT and is easily differentiated from congenital cryptorchidism if scrotal testicular position has been documented since birth. The prevalence of acquired cryptorchidism is 1–7% and peaks around 8 years of age.[13] The observation that acquired cryptorchidism is more common in boys with a history of proximal hypospadias suggests that a common mechanism, such as aberrant

androgen signaling, may predispose to both anomalies in otherwise normal boys.[14] Additionally, boys with a history of retractile testes may be at increased risk for testicular ascent.[11,14] Reports indicate that the same adverse histologic features (e.g. loss of germ cells) found in primary UDTs are also found in acquired cryptorchid testes.[15]

5. Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development. (*Standard; Evidence Strength: Grade A*)

Approximately 20–30% of all patients with cryptorchidism have bilateral UDTs.[4] In this situation, it is critical to determine if the gonads are palpable or nonpalpable. A newborn with a male phallus and bilateral nonpalpable gonads is potentially a genetic female (46 XX) with congenital adrenal hyperplasia until proven otherwise. Failure to diagnose congenital adrenal hyperplasia can result in serious harm, as a high proportion of patients with this condition are unable to regulate their electrolyte levels and may present with shock, hyponatremia and hyperkalemia.[16] Thus, serum electrolytes should be monitored. Additionally, karyotype and a hormonal profile (including 17-hydroxyprogesterone levels, luteinizing hormone, follicle-stimlating hormone, testosterone and androstenedione) must be obtained with simultaneous consultation with pediatric endocrinology and pediatric urology. Although the initial electrolyte evaluation can be obtained by the first-line provider, consultation with above specialists should be obtained due to the complexity of the condition and the need for coordinated multi-specialty care.

6. Providers should not perform ultrasound or other imaging modalities in the evaluation of boys with cryptorchidism prior to referral, as these studies rarely assist in decision making. (*Standard; Evidence Strength: Grade B*)

In the hands of an experienced provider or specialist, more than 70% of cryptorchid testes are palpable by physical examination and need no imaging. In the remaining 30% of cases with a nonpalpable testis, the challenge is to confirm absence or presence of the testis. At this time, there is no radiological test that can conclude with 100% accuracy that a testis is absent. Therefore, a surgical exploration, such as diagnostic laparoscopy (or open exploration), must be performed on all nonpalpable unilateral and most bilateral cryptorchid patients.

US is non-contributory in routine use, with sensitivity and specificity to localize a nonpalpable testis at 45% and 78%, respectively.[17] US cannot reliably localize a nonpalpable testis or confirm an absent/vanished testis. The cost and ionizing radiation exposure associated with CT scanning precludes its use. MRI with or without angiography has been more widely used with greater sensitivity and specificity but is deterred by cost, low availability and need for anesthesia.[18]

7. Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (*Recommendation; Evidence Strength: Grade C*)

A newborn boy with bilateral nonpalpable testes must be evaluated for disorder of sexual development and should not be circumcised until after the workup is complete, even if a completely normal phenotypic penis is documented on examination. A 46 XX individual with severe congenital adrenal hyperplasia can be mistaken for a boy with bilateral cryptorchidism. The possibility of DSD, or other syndromes should also be entertained when unilateral or bilateral cryptorchidism is present with phallic anomalies, such as hypospadias or micropenis.

8. In boys with bilateral, nonpalpable testes who do not have congenital adrenal hyperplasia, providers should measure müllerian inhibiting substance or anti-müllerian hormone and consider additional hormone testing to evaluate for anorchia. (*Option; Evidence Strength: Grade C*)

Masculinized infants with bilateral nonpalpable testes require prompt careful consideration and testing. Partially or completely masculinized infants with bilateral nonpalpable testes must be rapidly evaluated for 46 XX DSD due to life-threatening congenital adrenal hyperplasia (discussed above).

In contrast, if the infant with bilateral nonpalpable testes has normal penile development or micropenis and 46 XY karyotype, an evaluation to distinguish vanishing testis syndrome (bilateral congenital anorchia) versus bilateral abdominal testes is warranted. The latter is approximately 20 times more frequent than bilateral anorchia.[19] In order to avoid surgical exploration in the 46 XY male with anorchia, studies to assess for the presence of any viable testicular tissue should include serum MIS and additional hormone testing (inhibin B, FSH, LH, and testosterone) should be considered.

Within the testis, Leydig cells respond to endogenous LH or exogenous hCG by producing testosterone, while Sertoli cells respond to endogenous FSH by producing MIS and inhibin B. In infants with anorchia, the postnatal testosterone surge will be absent. In the recent past, intramuscular injections of hCG with serum testosterone levels (hCG stimulation test) were recommended in the evaluation of bilateral nonpalpable testes to assess

for Leydig cell function or absence. The failure of testosterone to increase after hCG stimulation alone is not diagnostic of anorchia; testicular dysgenesis with UDT may fail to respond to hCG stimulation. If the hCG stimulation test is used, it must be confirmed with a significant elevation in serum FSH and LH.

If the patient has anorchia and is less than 12 months of age, serum LH is high, FSH is high, MIS and inhibin B are undetectable, and testosterone is low. While the utility of hCG stimulation testing remains disputed, most recent studies suggest that a phenotypic 46 XY male with bilateral nonpalpable testes has isolated anorchia if undetectable levels of MIS and inhibin B with an elevated FSH level are present,[20] making neither hCG stimulation testing nor surgical exploration necessary for the diagnosis of isolated anorchia.[21] If the endocrine markers of Sertoli and Leydig cell function are normal, then testicular tissue is present despite being not palpable and surgical exploration is necessary.

9. In boys with retractile testes, providers should assess the position of the testes at least annually to monitor for secondary ascent. (*Standard; Evidence Strength: Grade B*)

Studies have reported an extremely broad range of incidence of testicular ascent out of the scrotum (between 2-45%) in boys with retractile testes.[11,22] It has been well documented that retractile testes are at increased risk for testicular ascent[22] which may be mechanistically related to the presence of a hyperactive cremasteric reflex, foreshortened patent processus vaginalis or entrapping adhesions.

Treatment

10. Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy. (*Standard; Evidence Strength: Grade B*)

Hormones to induce descent. Primary hormonal therapy with hCG or luteinizing hormone-releasing hormone or gonadotropin-releasing hormone has historically been used for many years, mostly in countries other than the United States.

hCG stimulates production of androgens by the Leydig cells. The action of hCG is virtually identical to that of pituitary LH although hCG appears to have a small degree of FSH activity as well. It stimulates production of androgens by the Leydig cells. Although an individual study on the efficacy of hCG may show a reasonable effect in inducing testicular descent, the overall review of all available studies fails to document long-term efficacy, and a significant risk of recurrence.[23,24] Success rates for descent into the scrotum are 25–55% in uncontrolled studies, but decrease to only 6–21% in randomized, blinded studies. Distal inguinal testes in older boys are more likely to descend in response to hormonal treatment than abdominal testes. Side effects of hCG treatment seen in up to 75% of boys include increased scrotal rugae, pigmentation, pubic hair, and penile growth, which may regress after treatment cessation. A total dose of more than 15,000 IU of hCG must be avoided since it may induce epiphyseal plate fusion and retard future somatic growth.[25]

LHRH analogs stimulate the release of the pituitary gonadotropins LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Success rates in uncontrolled studies range from 13-78% while better controlled investigations resulted in 6-38% success.[26,27] The recognized side effects of LHRH/GnRH (increased androgens, including increased penile or testicular size, scrotal erythema, or erections) seem to be less than seen with hCG. No long-term evaluation of LHRH treatment was done. For hCG and GnRH it has been reported that hormonal treatment may harm the germ cells in one to three-year old cryptorchid boys who did not respond to the hormones used to induce testicular descent.[28]

Hormones to improve fertility. No reports on long-term fertility outcomes following isolated hormonal therapy (no surgery at any time) were found in our literature search. Hormonal therapy may have value to optimize germ cell maturation and/or sperm production. LHRH or hCG administration prior to orchidopexy has been shown to improve the fertility index on biopsies obtained at the time of orchidopexy.[29]

11. In the absence of spontaneous testicular descent by six months (corrected for gestational age), specialists should perform surgery within the next year. (*Standard; Evidence Strength: Grade B*)

In a 10-year, retrospective study of 1,235 consecutive boys with cryptorchidism referred to pediatric urology practice, all patients with eventual spontaneous descent initially presented by six months (corrected for gestational age). Of those boys initially presenting beyond age six months no patient had spontaneous testicular descent.[4]

Orchidopexy in the first 18 months of life is recommended to preserve available fertility potential. In the majority of cases the total number of germ cells is within the normal range in cryptorchid testes during the first six months of life, but about 25% of the cryptorchid boys are born with a reduced number of germ cells.[30] After 15-18 months of age, some cryptorchid boys lack germ cells in the testes

and the number of boys without germ cells in a testicular biopsy increases to about 40% in bilateral cryptorchid boys at 8–11 years of age.

12. In prepubertal boys with palpable, cryptorchid testes, surgical specialists should perform scrotal or inguinal orchidopexy. (*Standard; Evidence Strength: Grade B*)

While it is optimal to perform surgery for the cryptorchid testis by 18 months of age, there are clear benefits to performing orchidopexy in all prepubertal boys at the time of diagnosis of a cryptorchid testis.[31] With regard to fertility, there has not been any direct assessment or long-term follow-up of patients with early v. late orchidopexy. Even though progressive and adverse histologic changes will occur in the cryptorchid testis prior to puberty, there may be fertility benefits that can still be realized with surgical correction of the cryptorchid testis prior to puberty.[32,33] It is widely recognized that the cryptorchid testis is associated with an inherent risk of malignant degeneration. Early reports of this increased risk were likely overestimated and recent review of the literature suggests that the overall relative risk is 2.75–8.[31] Prepubertal orchidopexy results in a two- to six-fold reduction in the relative risk compared with postpubertal orchidopexy. In the post pubertal child with cryptorchidism, consideration should be given to performing an orchiectomy or biopsy, although there needs to be careful consideration of other factors including associated medical conditions, anesthetic risk, and status of the contralateral testis.[31] Further discussion of the adult with cryptorchidism is beyond the scope of this guideline.

Recent studies that have evaluated open surgical intervention for the cryptorchid testis, even with inclusion of testes that are intra-abdominal, the overall success has been documented to be greater than 96% (range from 89–100%) (table 1). Subsequent atrophy of the testis is very uncommon and reported to be less than 2% (table 2).

For the palpable testis that is low lying, single incision orchidopexy is also a viable option. This primary scrotal approach was introduced by Bianchi and Squire[34] and has since gained widespread use and has been documented in retrospective studies to be equally effective as two incision orchidopexy in selected patients with testes located distal to the external inguinal ring that can be mobilized adequately via a scrotal incision.

13. In prepubertal boys with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. (*Standard; Evidence Strength: Grade B*)

A thorough examination should be performed following induction of general anesthesia to further determine if a testis is palpable. If the testis is palpable, open orchidopexy should be undertaken. However, if the testis remains nonpalpable, then a decision needs to be made to either pursue laparoscopic or open exploration. Previous studies evaluating laparoscopy for determining the location of the testicle have reported similar findings to open exploration.[43] Depending on the training and comfort level of the individual surgeon with laparoscopic techniques, open surgical management of the intra-abdominal testis is also appropriate given the lack of evidence to demonstrate that laparoscopic techniques have distinct advantages over open techniques with respect to success of the orchidopexy itself.[44,45]

If an intra-abdominal testis is found with anatomy that is felt to be appropriate for salvage, one of three surgical options can be chosen. The three types of surgical repair that one may consider are primary orchidopexy, one-stage Fowler-Stephens orchidopexy, and two-stage FS orchidopexy. Extensive review of previous studies evaluating the effectiveness of these procedures reveals that the success rate for all three approaches exceeds 75%, with an overall reported rate of 96.4% for primary orchidopexy, 78.7% for one-stage FS, and 86% for two-stage FS. While initial review of these success rates may suggest that primary orchidopexy is superior to the two other FS approaches, one must take into account

Table 1. *Success rates after orchidopexy for nonpalpable testes (open or laparoscopic, mixed techniques-primary, 1 or 2-stage Fowler-Stephens)*

References/Country	Quality	Total No. Participants/Techniques	Total No. Testicles	% Success (No. testicles treated)
Stec et al/United States[35]	Good	136/open or laparoscopic	156	89.1 (92)
Baker et al/United States[36]	Poor	226/laparoscopic	263	97.2 (178)
Chang et al/United States[37]	Poor	80/laparoscopic	92	100 (66)
Denes et al/Brazil[8]	Poor	46/laparoscopic	54	96 (26)
Dhanani et al/United States[38]	Poor	74/open or laparoscopic	83	100 (28)
Kim et al/South Korea[39]*	Poor	67/laparoscopic	86	98 (49)
Moursy et al/Egypt[40]	Poor	66/laparoscopic	76	100 (28)
		Total: 695	Total: 810	Pooled % 96.4

* Controlled for location, and all studies were of retrospective cohorts.

Table 2. *Atrophy rates after orchidopexy for nonpalpable testes*

References/Country	Quality	Total No. Participants	Total No. Testicles	% Atrophy (No. testicles treated)
Baker et al/United States[36]	Poor	226	263	2.2 (178)
Denes et al/Brazil[8]	Poor	46	54	4 (26)
Humphrey et al/United Kingdom[41]	Poor	48	20	0 (8)
Moursy et al/Egypt[40]	Poor	66	76	0 (33)
Radmayr et al/Austria[42]	Poor	84	57	0 (28)
		Total: 470	Total: 470	Pooled % 1.83

that all of these studies are observational cohorts and are limited by selection bias, confounding by indication and lack of randomization of the surgical techniques in many of the studies.

14. At the time of exploration for a nonpalpable testis in boys, surgical specialists should identify the status of the testicular vessels to help determine the next course of action. (*Clinical Principle*)

The identification of the testicular vessels should be the objective of any exploration for a nonpalpable testis. As previously mentioned in the guideline, radiologic imaging is typically not helpful in this situation because of its lack of both sensitivity and specificity for the identification of an abdominal testis. Regardless of surgical approach, the objective of the procedure is the same, which is to either identify the previously nonpalpable testis or identify the termination of the testicular vessels (no testis formation). The testicular vessels may end blindly anywhere along the course of descent of the testis. The exact location may range from the retroperitoneum along the psoas, the inguinal canal or commonly the scrotum itself.

15. In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. (*Clinical Principle*)

When operating on an abdominal testis, situations may arise when the patient has an atretic and/or short vas deferens, very short testicular vessels that place the testis high within the retroperitoneum, a dysmorphic testis or a testis in a postpubertal male. In these situations, an orchiectomy may be prudent in the presence of a normal contra-lateral descended testis. Another option for treatment is autotransplant of the undescended testis, however this has been done sparingly.[46]

16. Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (*Clinical Principle*)

There are two major long-term concerns for patients with a history of cryptorchidism: an increased incidence of developing testicular cancer and a heightened risk of subfertility.

Testicular Malignancy. Early reports stated a significantly higher risk of carcinoma in an abdominal testis; however, inclusion of boys with abnormal karyotype and/or genitalia may have confounded the results [49/100,000 (0.05%) to 12/1,075 (1%)]; however, inclusion of boys with abnormal karyotype and/or genitalia may have confounded the results.[47] Recent high quality studies have demonstrated that orchidopexy performed before puberty decreases the risk of testis cancer compared to those boys with cryptorchidism who undergo orchidopexy after puberty. The previously cryptorchid boy should be taught how to perform a monthly testicular self-examination after puberty to potentially facilitate early cancer detection.

Fertility. Formerly bilateral cryptorchid men have greatly reduced fertility compared with men with a history of unilateral cryptorchidism and the general male population.[48] One retrospective study showed a paternity rate of 62% (38% infertile) in formerly bilaterally cryptorchid men compared with a matched control group of 94% (6% infertile), indicating a six fold increased risk.[49] In contrast, unilaterally cryptorchid men had a paternity rate of 89.5%, which is similar to the level of fertility found in other studies of the general population (94%). Examination of subfertility, or time to pregnancy, shows that bilaterally cryptorchid men have greatly increased waiting times to pregnancy (33.9 months compared with 11.1 months for unilateral UDTs and controls). An assessment of paternity among men with monorchidism, whether as a result of an absent testis or orchiectomy, found no difference compared with those with unilateral cryptorchidism or control men.[50] Total germ cell count via biopsy at orchidopexy was not associated with significant changes in hormone levels or semen analysis results in adulthood, but adult dark spermatogonia counts were more significant. Testis biopsy at orchidopexy may have limited use in predicting future fertility in unilateral UDT but may be more clinically useful in predicting fertility potential for those with bilateral UDTs.

For boys with bilateral UDTs in whom no germ cells were found on biopsy, there was approximately

a 75 to 100% risk of infertility.[30] For unilateral UDTs, a lack of germ cells in testicular biopsies taken at surgery was associated with approximately 33% risk of later infertility.

Disclaimer

This document was written by the Evaluation and Treatment of Cryptorchidism Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2013. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists and other clinicians with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of cryptorchidism.

Funding of the committee was provided by the AUA. Committee members received no remuneration for their work. Each member of the committee provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration, or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

Conflict of Interest Disclosures

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received. **Consultant or Advisor: Peter A Lee,** Novo Nordisk (C), AbbVie, Inc. (C); **Meeting Participant or Lecturer: Earl Y. Cheng,** Salix (C); **Peter A Lee,** Novo Nordisk (C), AbbVie, Inc. (C); **Scientific Study or Trial: Thomas F. Kolon,** NIH (C); **Julia S. Barthold:** NIH (C); **Linda A. Baker:** NIH (C); **Earl Y. Cheng,** NIH (U), Allergan (U); **Peter A Lee,** Novo Nordisk (C), AbbVie, Inc. (C); **Leadership Position: Peter A Lee,** Pediatric Endocrine Society (U); **Other: Mireya Diaz,** Henry Ford Hospital - Vattikuti Urology Institute (C).

REFERENCES

1. Barteczko KJ and Jacob MI: The testicular descent in human. Origin, development and fate of the gubernaculum Hunteri, processus vaginalis peritonei, and gonadal ligaments. Adv Anat Embryol Cell Biol 2000; **156:** III.
2. Sampaio FJ and Favorito LA: Analysis of testicular migration during the fetal period in humans. J Urol 1998; **159:** 540.
3. Sijstermans K, Hack WW, Meijer RW et al: The frequency of undescended testis from birth to adulthood: a review. Int J Androl 2008; **31:** 1.
4. Berkowitz GS, Lapinski RH, Dolgin SE et al: Prevalence and natural history of cryptorchidism. Pediatrics 1993; **92:** 44.
5. Scorer CG: The descent of the testis. Arch Dis Child 1964; **39:** 605.
6. Berkowitz GS, Lapinski RH, Godbold JH et al: Maternal and neonatal risk factors for cryptorchidism. Epidemiology 1995; **6:** 127.
7. Smolko MJ, Kaplan GW and Brock WA: Location and fate of the nonpalpable testis in children. J Urol 1983; **129:** 1204.
8. Denes FT, Saito FJ, Silva FA et al: Laparoscopic diagnosis and treatment of nonpalpable testis. Int Braz J Urol 2008; **34:** 329.
9. Bright Futures/American Academy of Pediatrics: Recommendations for preventative pediatric health care. 2014.
10. Rusnack SL, Wu HY, Huff DS et al: Testis histopathology in boys with cryptorchidism correlates with future fertility potential. J Urol 2003; **169:** 659.

11. Stec AA, Thomas JC, DeMarco RT et al: Incidence of testicular ascent in boys with retractile testes. J Urol 2007; **178:** 1722.
12. Surgical Advisory Panel: Referral to pediatric surgical specialists. Pediatrics 2014; **133:** 350.
13. John Radcliffe Hospital Cryptorchidism Study Group: Cryptorchidism: a prospective study of 7500 consecutive male births, 1984-8. Arch Dis Child 1992; **67:** 892.
14. Tasian GE, Zaid H, Cabana MD et al: Proximal hypospadias and risk of acquired cryptorchidism. J Urol 2010; **184:** 715.
15. Rusnack SL, Wu HY, Huff DS et al: The ascending testis and the testis undescended since birth share the same histopathology. J Urol 2002; **168:** 2590.
16. White PC: Neonatal screening for congenital adrenal hyperplasia. Nat Rev Endocrinol 2009; **5:** 490.
17. Tasian GE and Copp HL: Diagnostic performance of ultrasound in nonpalpable cryptorchidism: a systematic review and meta-analysis. Pediatrics 2011; **127:** 119.
18. Kanemoto K, Hayashi Y, Kojima Y et al: Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of non-palpable testis. Int J Urol 2005; **12:** 668.
19. Boisen KA, Kaleva M, Main KM et al: Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. Lancet 2004; **363:** 1264.
20. Brauner R, Neve M, Allali S et al: Clinical, biological and genetic analysis of anorchia in 26 boys. PloS one 2011; **6:** e23292.
21. Teo AQ, Khan AR, Williams MP et al: Is surgical exploration necessary in bilateral anorchia? J Pediatr Urol 2013; **9:** e78.
22. Barthold JS and Gonzalez R: The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy. J Urol 2003; **170:** 2396.
23. Hocht B: LH-RH treatment for cryptorchidism: randomized study and 10-year follow-up results. Eur J Pediatr 1987; **146:** S44.
24. Waldschmidt J, el-Dessouky M and Priefer A: Therapeutic results in cryptorchidism after combination therapy with LH-RH nasal spray and hCG. Eur J Pediatr 1987; **146:** S31.
25. Hjertkvist M, Läckgren G, Plöen L et al: Does hCG treatment induce inflammation-like changes in undescended testes in boys. J Pediatr Surg 1993; **28:** 254.
26. Waldschmidt J, Doede T and Vygen I: The results of 9 years of experience with a combined treatment with LH-RH and HCG for cryptorchidism. Eur J Pediatr 1993; **152** (suppl 2): S34.
27. Lala R, Matarazzo P, Chiabotto P et al: Combined therapy with LHRH and HCG in cryptorchid infants. Eur J Pediatr 1993; **152** (suppl 2): S31.
28. Cortes D, Thorup J and Visfeldt J: Hormonal treatment may harm the germ cells in 1 to 3-year old cryptorchid boys. J Urol 2000; **163:** 1290.
29. Schwentner C, Oswald J, Kreczy A et al: Neoadjuvant gonadotropin-releasing hormone therapy before surgery may improve the fertility index in undescended testes: a prospective randomized trial. J Urol 2005; **173:** 974.
30. Cortes D, Thorup JM and Beck BL: Quantitative histology of germ cells in the undescended testes of human fetuses, neonates and infants. J Urol 1995; **154:** 1188.
31. Wood HM and Elder JS: Cryptorchidism and testicular cancer: separating fact from fiction. J Urol 2009; **181:** 452.
32. Miller KD, Coughlin MT and Lee PA: Fertility after unilateral cryptorchidism. Paternity, time to conception, pretreatment testicular location and size, hormone and sperm parameters. Horm Res 2001; **55:** 249.
33. McAleer IM, Packer MG, Kaplan GW et al: Fertility index analysis in cryptorchidism. J Urol 1995; **153:** 1255.
34. Bianchi A and Squire BR: Trans-scrotal orchidopexy: orchidopexy revised. Pediatr Surg Int 1989; **4:** 189.
35. Stec AA, Tanaka ST, Adams MC et al: Orchiopexy for intra-abdominal testes: factors predicting success. J Urol 2009; **182:** 1917.
36. Baker LA, Docimo SG, Surer I et al: A multi-institutional analysis of laparoscopic orchidopexy. BJU Int 2001; **87:** 484.
37. Chang B, Palmer LS and Franco I: Laparoscopic orchidopexy: a review of a large clinical series. BJU Int 2001; **87:** 490.
38. Dhanani NN, Cornelius D, Gunes A et al: Successful outpatient management of the nonpalpable intra-abdominal testis with staged Fowler-Stephens orchiopexy. J Urol 2004; **172:** 2399.
39. Kim J, Min GE and Kim KS: Laparoscopic orchiopexy for a nonpalpable testis. Korean J Urol 2010; **51:** 106.
40. Moursy EE, Gamal W and Hussein MM: Laparoscopic orchiopexy for non-palpable testes: outcome of two echniques. J Pediatr Urol 2011; **7:** 178.
41. Humphrey GM, Najmaldin AS and Thomas DF: Laparoscopy in the management of the impalpable undescended testis. Br J Surg 1998; **85:** 983.
42. Radmayr C, Oswalk J, Schwentner C et al: Long-term outcome of laparoscopically managed nonpalpable testes. J Urol 2003; **170:** 1463.
43. Chandrasekharam VV: Laparoscopy vs inguinal exploration for nonpalpable undescended testis. Indian J Pediatr 2005; **72:** 1021.
44. Escarcega-Fujigaki P, Rezk GHP, Huerta-Murrieta E et al: Orchiopexy-laparoscopy or traditional surgical technique in patients with an undescended palpable testicle. J Laparoendosc Adv Surg Tech 2011; **21:** 185.
45. Steinhardt GF, Kroovand RL and Perlmutter AD: Orchiopexy: planned 2-stage technique. J Urol 1985; **133:** 434.
46. Bukowski TP, Wacksman J, Billmire DA et al: Testicular autotransplantation: a 17-year review of an effective approach to the management of the intra-abdominal testis. J Urol 1995; **154:** 558.
47. Johnson D, Woodhead D, Pohl D et al: Cryptorchidism and tumorigenesis. Surgery 1968; **63:** 919.
48. Gracia J, Sánchez Zalabardo J, Sánchez García J et al: Clinical, physical, sperm and hormonal data in 251 adults operated on for cryptorchidism in childhood. BJU Int 2000; **85:** 1100.
49. Lee PA, O'Leary LA, Songer NJ et al: Paternity after unilateral cryptorchidism: a controlled study. Pediatrics 1996; **98:** 676.
50. Lee PA and Coughlin MT: A single testis: Paternity assessment after presentation as unilateral cryptorchidism. J Urol 2002; **168:** 1680.