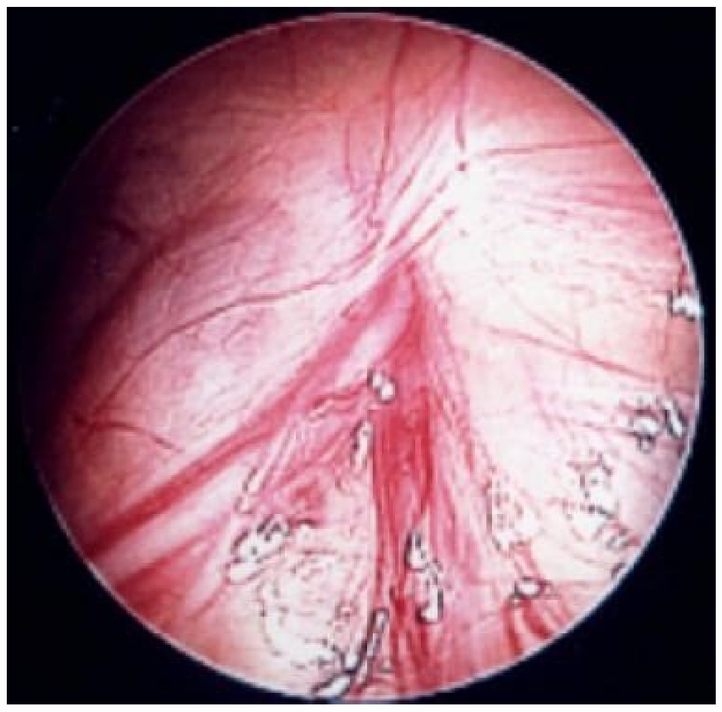
Aua guideline cryptorchidism



13. Prepubertal hastalarda anestezi altında tekrar muayene yap, palpe edilemezse cerrahi eksplorasyon (Standart,B)
    - Palpe edilirse açık orşiopeksi
    - Palpe edilemezse açık/lap testis aranması.
        - Açık testis aranması ile laparoskopi arasında benzer oranlar.
14. Cerrahi eksplorasyonda testiküler damarlar ortaya çıkarılmalıdır.(Klinik Prensip)
    - Bir sonraski adımda yardımcı olur.
    - Ya testisi bul, ya da testiküler yapının sonunu bul.

Commentary

AUA Guideline on the Diagnosis and Treatment of Cryptorchidism

Cryptorchidism is one of the most common male pediatric urological conditions, and one that can have a lifelong effect if not managed appropriately. The evaluation and treatment of cryptorchidism have progressed significantly during the last several decades, as the condition has been studied extensively. While we now have a much better understanding of the pathogenesis and sequelae of undescended testes (UDTs), our knowledge remains incomplete. Given the breadth of studies performed in the last 3 decades examining the many pathogenetic factors contributing to cryptorchidism, as well as the availability of numerous hormonal and surgical treatment options, a comprehensive consensus statement was necessary. This consensus document is now presented as the American Urological Association guideline on the evaluation and treatment of cryptorchidism.

The purpose of this complementary commentary is to inform the reader on progress in the evaluation and treatment of cryptorchidism since March 2013, the last time when studies pertinent to the development of the guideline were evaluated. Additionally, given that the risk of malignancy in men with a history of cryptorchidism is not as high as previously thought, we briefly discuss considerations in postpubertal males with a history of cryptorchidism, which were not addressed in the guideline.

To identify salient studies to include in this commentary, we searched PubMed® for articles related to cryptorchidism in children and adults, limited to humans, between March 2013 and April 2014. In our review we focused on reports that provided additional data to enhance the conclusions of the AUA guideline panel. We identified work in numerous areas focused on in the guidelines about which additional findings had been reported, including epidemiology, genetics, environmental factors, use of imaging, hormonal and surgical treatment, natural course of cryptorchidism and fertility.

EPIDEMIOLOGY

A clear distinction is now made between congenital and acquired cryptorchidism. In the AUA guideline several studies evaluated testicular ascent among boys with descended testes at birth, finding that approximately 23% of testes ascended, resulting in acquired cryptorchidism. A more recent study retrospectively evaluated the records 660 boys who underwent orchiopexy after age 2 years, of whom 66% had a scrotal testis on 2 or more occasions and suggesting a significantly higher ascent rate than previously observed.[1] Furthering the relationship between cryptorchidism and disorders of sexual differentiation, a recent report identified a link between prematurity and intrauterine growth retardation in boys with hypospadias and UDT, adding to the list of risk factors for UDT and indications for a multidisciplinary evaluation.[2]

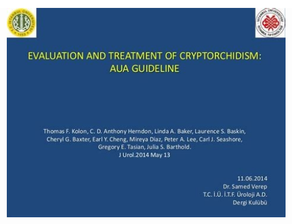
CRYPTORCHIDISM GENETICS

Evidence supporting genetic susceptibility in boys with UDT is currently weak, although several genes including *INSL3*, *LGR8*, *AR* and *ESR1* have been implicated. More recently, the anti-müllerian hormone (AMH) receptor type 2 has been correlated with UDT, as it was found to be expressed in 100% of 109 appendix testes from patients with UDT.[3] A recent case report describing a case of persistent müllerian duct syndrome with an undetectable AMH level demonstrated a novel T>G base substitution in the *AMH* gene, resulting in a Leu>Arg amino acid change.[4] Given that testicular descent is affected by AMH, these findings suggest a role for it and its receptor in the pathogeneses of UDT.

Novel work has also linked deletion of the distal portion of chromosome 9p to cryptorchidism and other urological anomalies, identifying *DMRT1* as the likely responsible gene.[5] Finally, a new *AR* mutation (c.2214 T>G; Ile>Met) was identified in a family with testicular dysgenesis syndrome which was found to decrease AR transcriptional activity by 50%, in line with the concept that reduced androgen signaling might contribute to the development of the syndrome.[6] Similar to the genes discussed in the AUA guideline, the aforementioned genes lack proof of causality in linking them to UDT.

0022-5347/14/1922-0346/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.05.007
Vol. 192, 346-349, August 2014
Printed in U.S.A.



Aua varicocele guidelines. Evaluation and treatment of cryptorchidism aua guideline. Aua guidelines testicular torsion. Aua guidelines cryptorchidism. Cryptorchidism guidelines.

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. Keywords: cryptorchidism; hormone; infertility; testis cancer; undescended testis. Home Guidelines Guidelines Clinical Guidelines Cryptorchidism Guideline Thomas F. Kolon, C. D. Anthony Herndon, Linda A. Baker, Laurence S. Baskin, Cheryl G. Baxter, Earl Y. Cheng, Mireya Diaz, Peter A. Lee, Carl J. Seashore, Gregory E. Tasian, Julia S. Barthold Cryptorchidism or undescended testis (UDT) is one of the most common pediatric disorders of the male endocrine glands and the most common genital disorder identified at birth. The main reasons for treatment of cryptorchidism include increased risks of impairment of fertility potential, testicular malignancy, torsion and/or associated inguinal hernia. Cryptorchidism has evolved significantly over the past half century, with respect to both diagnosis and treatment. The current standard of therapy in the United States is orchidopexy (also referred to as orchiopexy in the literature), 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. The panel members are representative of various medical specialties (pediatric urology, pediatric endocrinology, general pediatrics).MethodsThe primary source of evidence for this guideline was the systematic review conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review titled Evaluation and Treatment of Cryptorchidism (2012). That report included rigorous searches of MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and EMBASE for English-language studies published from January 1980 through February 2012 relevant to cryptorchidism. To capture more recently published manuscripts and expand the body of evidence provided in the original AHRQ report, the American Urological Association (AUA) 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 sources yielded 704 studies, after exclusions, that were used to inform the statements presented in the guideline as Standards, Recommendations or Options. 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. In 2018, this guideline underwent its first update literature review (ULR) where new evidence using the same methodology developed a priori from the original guideline were evaluated. The search period for the ULR extended from March 2013 to October 2018. A total of 93 references were included in the ULR evidence base, with the ULR panel finding no sufficient new evidence to alter existing guideline statements or to develop new ones. Additional supporting data were however added to the bibliography of the present guideline to emphasize the importance of counseling expectant and new parents about the potential risk of cryptorchidism associated with certain maternal risk factors.Guideline StatementsDiagnosis1. Providers should obtain gestational history at initial evaluation of boys with suspected cryptorchidism. (Standard; Evidence Strength: Grade B)2. Primary care providers should palpate testes for quality and position at each recommended well-child visit. (Standard; Evidence Strength: Grade B)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)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)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 (DSD). (Standard; Evidence Strength: Grade A)6. Providers should not perform ultrasound (US) 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)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)8. In boys with bilateral, nonpalpable testes who do not have congenital adrenal hyperplasia (CAH), providers should measure Müllerian Inhibiting Substance (MIS or Anti- Müllerian Hormone [AMH]) level), and consider additional hormone testing, to evaluate for anorchia. (Option; Evidence Strength: Grade C)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)Treatment10. 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)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)12. In prepubertal boys with palpable, cryptorchid testes, surgical specialists should perform scrotal or inguinal orchidopexy. (Standard; Evidence Strength: Grade B)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)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)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)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) Cryptorchidism or undescended testis (UDT) is one of the most common pediatric disorders of the male endocrine glands and the most common genital disorder identified at birth. The main reasons for treatment of cryptorchidism include reducing the risks of impairment of fertility potential, testicular malignancy, torsion and/or associated inguinal hernia. Cryptorchidism has evolved significantly over the past half century, with respect to both diagnosis and treatment. The current standard of therapy in the United States is orchidopexy (also referred to as orchiopexy in the literature), 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 all of 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. The panel members are representative of various medical specialties (pediatric urology, pediatric endocrinology, general pediatrics).MethodologyQuality of Studies and Determination of Evidence Strength. The primary source of evidence for this guideline was the systematic review conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review titled Evaluation and Treatment of Cryptorchidism (2012). That report included rigorous searches of MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and EMBASE for English-language studies published from January 1980 through February 2012 relevant to cryptorchidism. To capture more recently published manuscripts and expand the body of evidence provided in the original AHRQ report, the American Urological Association (AUA) 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 sources yielded 704 studies, after exclusions, that were used to inform the statements presented in the guideline as Standards, Recommendations or Options. Quality of individual studies was rated as high, moderate, or low based on instruments tailored to specific study designs. Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool.1 Conventional diagnostic cohort studies, diagnostic case-control studies, or diagnostic case series that presented data on diagnostic test characteristics were evaluated using the QUADAS-2 tool2 that evaluates the quality of diagnostic accuracy studies. Cohort studies with a comparison of interest were evaluated with the Drug Effectiveness Review Project instrument.3 The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies) or Grade C (observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data). The quality of the evidence was variable depending on the issue examined. For many epidemiological issues there was a combination of moderate to large sized population-based studies, some of them prospective, being the key issue, as well as the consistency of findings. When evidence was consistent it was graded B, otherwise C. For issues related to management, studies tend to be non-randomized cohorts of moderate size or randomized trials of small to moderate size. Again the key issue was consistency of findings and the same criterion indicated above was applied. Seventy percent of the graded statements were considered level B (many under the AUA's premise of moderate quality, moderate certainty).AUA Nomenclature: Linking Statement Type to Evidence Strength. 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.4 Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. Options are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; the decision is based on full consideration of the patient's prior clinical history, current quality of life, preferences and values. Options may be supported by Grade A, B or C evidence.In some instances, the review revealed insufficient publications to address certain questions from an evidence basis; therefore, some statements are provided as Clinical Principles or as Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion emerged.5 A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel that is based on members' clinical training, experience, knowledge and judgment for which there is no evidence.Limitations of the Literature. Limitations of the literature identified by both the AHRQ and the AUA reviews include, (1) lack of studies assessing the value of hormonal stimulation testing, long-term fertility outcomes, as well as inconsistent reporting of age at diagnosis and/or at treatment; (2) scant information about imaging effectiveness for modalities other than ultrasound (US) and magnetic resonance imaging (MRI); (3) low level evidence for the effectiveness of surgical treatment other than primary orchidopexy, accompanied by a lack of a standardized definition of success, follow-up length, reporting of complications, and control of confounding variables by indication; (4) inconsistent control of confounding variables among studies evaluating the epidemiology of cryptorchidism. This could be the result of the remaining uncertainty with respect to the etiological factors strongly and consistently associated with cryptorchidism.Peer review. The AUA conducted an extensive peer review process. The initial draft of this Guideline was distributed to 84 peer reviewers of varying backgrounds, including those who applied through open comment; 43 responded with comments. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the Guideline was submitted for approval to the Practice Guidelines Committee (PGC). It was then submitted to the AUA Board of Directors for final approval.Update Literature Review. In 2018, this guideline underwent its first ULR where new evidence using the same methodology developed a priori from the original guideline were evaluated. The search period for the ULR extended from March 2013 to October 2018. A total of 93 references were included in the ULR evidence base, with the ULR panel finding no sufficient new evidence to alter existing guideline statements or to develop new ones. Additional supporting data were, however, added to the bibliography of the present guideline to emphasize the importance of counseling expectant and new parents about the potential risk of cryptorchidism associated with certain maternal risk factors. Cryptorchidism, or undescended testis (UDT), 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 accident.Congenital cryptorchidism refers to testes that are extrascrotal from the time of birth. Acquired cryptorchid testes are intrascrotal at birth but subsequently identified in an extrascrotal position. Cryptorchid testes may be prescrotal (above or at the scrotal inlet), in the superficial inguinal pouch (distal and lateral to the external inguinal ring, anterior to the rectus muscle), at the external ring (or prepubic), canalicular (within the inguinal canal), ectopic (most commonly perineal) or abdominal ("peeping" through or proximal to the internal inguinal ring, or near the bladder, iliac vessels or kidney).Acquired cryptorchid testes are considered ascending, when apparent change from an intrascrotal to an extrascrotal position occurs spontaneously at some point after birth, or entrapped, when such change occurs after prior inguinal surgery. A retractile testis is one that is initially extrascrotal on examination or moves easily out of scrotal position, (often associated with a vigorous cremasteric reflex), but that can be manually replaced in stable, dependent scrotal position and remain there without tension at least temporarily. An atrophic testis is one that suffers significant volume loss after prior inguinal or testicular surgery, or due to prolonged location in an extrascrotal position or primary developmental failure.EpidemiologyPrevalence/incidence of congenital v. acquired cryptorchidism. Although delayed diagnosis or treatment of cryptorchidism beyond the neonatal period is well-documented, the relative proportion of cases of true testicular ascent v. congenital cases that were not identified and/or referred early for care remains unclear. 6, 7, 8, 9 However, the preponderance of data strongly supports the existence of acquired cryptorchidism as a real phenomenon whose prevalence may be similar to that of congenital cryptorchidism. In a population-based health registry study, cryptorchidism was frequently diagnosed beyond the newborn period, and there were no age-specific differences in time between diagnosis and surgical correction.10 Similarly, in birth cohort studies,9, 11 suprascrotal testes were newly diagnosed in about 2% of boys examined longitudinally at intervals up to 10 years of age. Spontaneous descent of congenitally cryptorchid testes occurred in 35-43% of newborn boys followed longitudinally, usually prior to 3 months of age,9, 11, 12 but re-ascent (recurrent cryptorchidism) may occur, and was reported in 22% of boys in a recent prospective study.13 In a referral population, Wenzler et al.14 documented spontaneous descent in 24% of boys presenting prior to age 4 months and none presenting at or after 6 months, or a total of 6.9% of boys presenting in the first year of life. The overall rate of spontaneous descent in this latter study may be low because the referral population likely excluded cases of early postnatal spontaneous descent.Sijstermans et al.15 compiled a systematic review estimating the prevalence of cryptorchidism by different ages and birth weights (Table 1). They identified 97 articles, but only 49 remained eligible. These studies were conducted between 1934 and 2006. Thirty-eight studies (83%) were prospective, and the other eleven were retrospective, totaling over 704,000 males. Fifty percent of the studies used a formal definition to identify and diagnose cryptorchidism, although these definitions varied widely. Ten percent of articles used the definition by Scorer16 that considers all testes at least 4 cm below the pubic crest in full term males (2.5 cm in preterm males) as descended; 41% included location in the definition, and 13% excluded high scrotal testes.Table 1: Prevalence of cryptorchidism Study characteristicsEstimatesNewborn All 2.5 kg23 studies0.1-9.0% 1.1-45.3% 1.0-4.6%One month All 1.0-1.2%Three months All 2.5 kg7 studies0.7-1.9% 1.7-5.2% 0.9-1.6%One yearAll 2.5 kg6 studies1.1%-2.1% 1.9-7.3% 1.0-1.5%Three years 0.8-2.5%Six years Eight years Ten years Eleven years Thirteen years 0.0-2.6% 0.0-6.3% 0.0-3.6% 0.0-6.6% 0.0-4.0%*Adapted from 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.It can be seen that for boys up to one year of age and of normal weight, the estimates are rather stable, while for the same age range but low birth weight they vary widely. This age group constitutes 57% of the studies with over 591,000 infants. It is important to highlight, as indicated by the authors of the compendium, that low birth weight and prematurity were often used synonymously. The prevalence for boys three years and older is again rather stable between null and 6.6%. In addition to birth weight and prematurity, the authors indicate that the lack of distinction between congenital (never descended from birth) and acquired (previously scrotal) cryptorchidism may explain the differences in rates. The distinction between congenital and acquired cryptorchidism could not be made for the majority of these studies as only 5 (11%) of the studies reviewed included data documenting prior testicular position.In a large population-based study of 819,111 non-syndromic boys in Denmark, Jensen and colleagues analyzed associations between birth weight, prematurity and cryptorchidism, which occurred in 14.1 cases out of 1000 boys.17 When correcting birth weight for gestational age, only boys in the lowest quintile (1000V18M, P49S, W69R, R73X, T86M, P93L, R102C, R102H, R105H, N110KLGR8 1, 7, 20, 237 (2002-11)43/1474 (2.9%)16/2026 (0.8%)T222PTwo other potential candidate genes, androgen receptor (AR), and estrogen receptor alpha (ESR1) are involved in sex hormone function. Exon 1 of the AR gene encodes highly polymorphic polyglutamine (CAG) and polyglycine (GGN) repeat sequences. In vitro assays have demonstrated that CAG repeat expansion or GGN deletion is associated with diminished transcriptional activity of the receptor.24 Five different cohorts24-28 have examined the potential association between AR exonic repeats and cryptorchidism by testing the difference in the mean number of repeats between cases and controls (see evidence table in Appendix B). Three of these studies identified no differences in repeat length between cases and controls, one reported increased CAG repeat length in two small subgroups of Portuguese males (six bilateral cryptorchidism and seven unilateral with contralateral patent processus vaginalis),28 and the largest study reported reduced CAG repeats in Hispanic cryptorchid males from California.25 GGN repeat length was higher in cryptorchid cases than controls in one study.24For the ESR1 gene, efforts have focused on the potential difference in the frequency distribution of alleles A and G between cases and controls for SNP12 (rs6932902). This SNP12 has been labeled as the tag SNP of the 5-SNP haplotype AGATA. Such allele frequency distributions have been assessed in three independent groups of cases and controls from three different ethnic backgrounds with disparate results (see evidence table in Appendix C). The A allele has been found to confer susceptibility to Japanese men,29 (OR1.99, 95% CI 1.07, 3.67), seems protective among Caucasian men from Italy (OR 0.5, 95%CI 0.28, 0.90),30 and showed lack of association among a multi-ethnic US cohort.31 For the latter, the allele frequency for G was significantly different between moderate and severe cases (OR 10.0, 95% CI 1.2, 78.2).In summary, although there is some suggestion that the examined genomic loci may contribute to cryptorchidism susceptibility, the evidence is weak at this point and likely due to the multifactorial nature of the trait, the heterogeneous phenotypic manifestation of cryptorchidism as well as the lack of simultaneous assessment of potential gene-environment interactions.Familial AggregationTwo studies have explored the risk of UDT in an individual with a family history. Elert et al32 assessed the familial risk in a group of 374 cases and 374 controls in Germany. Cases were identified in boys and men who underwent surgery for UDT between 1989 and 2001. The mean age of these males at surgery was 6 years (range 1-39 years). They found that 85 cases (23%) v. 28 controls (7.5%) had one or more family members with UDT for an overall risk of 3.6 (95% CI 2.3, 5.7). The highest risk was present if the family member was a brother (95% CI 6.9 [2.7, 17.9]), followed by an uncle (95% CI 5.2 [1.8, 15.4]) and then by the father (95% CI 4.6 [2.0, 10.6]).The second study was a large population-based study conducted in Denmark between 1977 and 2005.33 Danish boys were identified from the Civil Registration Systems and their relatives from the Danish Family Relations Database. The cryptorchidism status was gathered from the Danish Hospital Discharge Register. Using these data sources, of 42,105 cases, 20,398 (48.5%) were confirmed surgically. The measure of risk the authors used is the recurrence risk ratio (RRR), the ratio between cryptorchidism prevalence for individuals with a proband (older affected relative) and the prevalence of cryptorchidism for individuals with known relatives of the same kind where none of them is a proband. For twin pairs, a weighted average contribution from dizygotic and monozygotic twins was applied. Given their almost equal distribution in this cohort, a weight of 0.5 was assigned for each. The RRR was 10.1 (95% CI: 7.78, 13.1) in twins, 3.52 (95% CI: 3.26, 3.79) in brothers, 2.31 (95% CI: 2.09, 2.54) in sons, 2.12 (95% CI: 1.74, 2.60) in maternal half-brothers and 1.28 (95% CI: 1.01, 1.61) in paternal half-brothers. This led the authors to conclude that the maternal contribution is greater than the paternal one, suggesting either an X-linked mode of inheritance or a combination of genetic factors and maternal environment. Elert et al.32 noted similar findings in a much smaller cohort study, but did not observe a difference in rates for maternal and paternal inheritance.Environmental Exposure. The possibility that environmental chemicals alter normal reproductive tract development has been debated in the recent literature. There is significant potential concern that endocrine-disrupting chemicals may be linked to male reproductive tract anomalies that may have a common etiology, including cryptorchidism (sometimes termed 'testicular dysgenesis syndrome').34, 35 Concerns for a connection between endocrine-disrupting chemicals and cryptorchidism developed because of a reported higher risk related to early maternal exposure to diethylstilbestrol (DES).Environmental ChemicalsA quantitative summary of the potential effect of exposure to pesticides and the risk of cryptorchidism is not possible because of the large variability on study designs, exposure and outcome assessment and measurement. Virtanen and Adamsson (2012)36 qualitatively summarized 18 studies in 2012. Two large ecological studies with adequate power found different results based on the pesticide use in the area; one a significant positive association and the other a non-significant positive association. Ten studies assessing exposure in terms of parental occupation, primarily in agriculture and gardening also had sufficient power. Outcomes differed with four studies indicating a positive significant association, three a non-significant association, and three studies reporting a decreased risk. Six studies assessed the exposure in terms of pesticide levels in biological specimens, assessing the exposure in a more direct fashion, but were inconclusive because of small sample size.There have been a number of case control studies assessing other chemicals such as polychlorinated biphenyls (PCBs), dioxins, flame retardants and phthalates. These studies have been of small sample size and have not demonstrated statistical significance.36-41Incidence seasonalityMamoulakis et al.42 examined the significance of seasonal trends in cryptorchidism incidence among over 209,000 live-born boys in Greece between 1995 and 1999. The incidence of cases at birth was cyclic with a peak in March (61.0) and a trough in September (36.1). After exclusions, 583 isolated true cryptorchid cases were identified. The authors reported that maternal hCG levels at 26 weeks gestation were lower in winter months and suggest that low environmental temperature may influence maternal hCG profiles and hence the inguinoscrotal phase of testicular descent. However, this finding is of questionable relevance as the authors did not compare hCG in pregnancies with and without cryptorchid fetuses, and hCG levels are normally very low after the first trimester.Three other studies were cited with a large number of cryptorchid cases conducted in European countries in which March is the month with peak incidence for cryptorchidism births. A fourth study in the United States of America found two peaks: one during September-November when a trough was observed in the other studies and a second smaller peak during March-May.Maternal environmentMaternal Body Mass Index (BMI)Adams et al.43 conducted a population-based case-control study using birth record data from the state of Washington during the period 1992-2008. The authors discuss three potential mechanisms relating maternal obesity to the risk of cryptorchidism and hypospadias. These are, (1) levels of circulating hormones, (2) lower overall diet quality and blood concentrations of micronutrients, (3) impaired fasting glucose and glucose tolerance before and during pregnancy. Five randomly selected controls from the same birth year were assigned to each of the 3,946 cases of cryptorchidism. Maternal BMI was missing in 30% of cases and 28% of controls. Cryptorchidism and hypospadias may be more common in first pregnancies. Maternal weight was collected from the birth certificates, while height was collected from the driver's licenses prior to 2003, and from the birth certificates from 2003 onwards. BMI was categorized using the World Health Organization (WHO) thresholds. No association between BMI and the incidence of cryptorchidism was found based on odds ratios adjusted for year of birth, maternal age, education, parity, race, and cigarette smoking during pregnancy. Based on a reference group of mothers with normal weight, the adjusted odds ratio for underweight mothers was 1.14 (95% CI 0.93, 1.39); for overweight 1.03 (95% CI 0.93, 1.14) and for obese mothers 0.99 (95% CI 0.89, 1.11). Similarly, no effect was observed when weight was analyzed as a continuous variable with changes measured per each 5 kg/m2, OR=1.01 (95% CI 0.97, 1.05).Maternal hypertensionArendt et al. conducted a population-based cohort study evaluating boys born between 1978 and 2012 who, along with their mothers had a valid personal identification number to enable the linking of long-term follow-up data with the Danish Medical Birth Register.44 By classifying their mothers into categories based on the presence of a hypertensive disorder in pregnancy identified using ICD-8, ICD-9 or ICD-10 codes, they were able to analyze the risk of cryptorchidism by types of hypertensive disorders in pregnancy, against a reference group of mothers who did not have any form of hypertension in pregnancy. A total of 5,098 boys were born to mothers who had pre-gestational hypertension, 9,283 boys were born to mothers who had gestational hypertension, 32,427 boys were born to mothers who had pre-eclampsia or eclampsia, including HELLP syndrome and 1,026,218 boys were born to mothers who had no hypertensive disorder in pregnancy. Pre-gestational hypertension (HR=1.3, 95% CI 1.1, 1.6), gestational hypertension (HR=1.2, 95% CI 1.1, 1.4), moderate pre-eclampsia (HR=1.2, 95% CI 1.1, 1.4), severe pre-eclampsia (HR=1.7, 95% CI 1.4, 2.0) and HELLP syndrome (HR=2.1, 95% CI 1.4, 3.2) were associated with a greater likelihood of cryptorchidism, after adjusting for maternal age at birth in years, parity, maternal years of education, maternal nationality, calendar year at birth and maternal diabetes, and accounting for clustering within families using robust standard errors. Further analysis was conducted to examine if timing of onset of pre-eclampsia/eclampsia influenced the risk of cryptorchidism. Pre-eclampsia or eclampsia occurring

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