Comparative Effectiveness Review
Number 88

Effective Health Care Program

# Evaluation and Treatment of Cryptorchidism

## *Executive Summary*

### Background

Cryptorchidism is a congenital condition in which one or both testicles are not appropriately positioned in the scrotum at birth and cannot be moved into the proper position manually. The term "cryptorchidism" literally means "hidden testicle" and is often used interchangeably with the term "undescended testicle."[1] It affects an estimated 3 percent of full-term male neonates and up to 30 percent of premature male infants, making it the most common male genital anomaly identified at birth.[2,3] The etiology of cryptorchidism is not well understood, and the undescended testicles may be palpable or nonpalpable. The undescended testicles may be present in the abdomen, in the groin area, or misplaced in the scrotum. In some cases they are viable testicles, but in others they have atrophied and are no longer viable. Finally, in some individuals no testicle exists at all (anorchia).

Cryptorchidism is often apparent to parents, and examination for the condition is part of general pediatric care. Therefore, boys with cryptorchidism are usually identified early in life, often within the first year. Clinical decisionmaking about treatment is influenced by many factors, including whether or not the testicle is palpable, whether the condition is present unilaterally or bilaterally, the age at

### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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presentation, and coexisting medical conditions. In boys under 1 year of age whose testicle is palpable and is close to, but not quite inside, the scrotum, it may be difficult to distinguish between "true" cryptorchidism and a retractile testicle. In this case, health care providers often elect to observe the patient's condition until he is 1 year old.

Although about 70 percent of cryptorchid testicles spontaneously descend within the first year of life, the number of boys with persistent undescended testicles remains constant at approximately 1 percent.[4,5] Between 1992 and 2000, there were more than 600,000 physician office visits among males under age 18 for which cryptorchidism was the primary diagnosis (96 per 100,000 visits).[2] Once cryptorchidism is diagnosed, treatment choices may include watchful waiting, hormonal treatment, or surgery. Decisions about which clinical pathway to follow may be guided by results of hormonal stimulation testing and/or imaging, particularly when the testicle is nonpalpable.

The purpose of hormonal stimulation testing for bilateral nonpalpable cryptorchidism is to determine if viable testicular tissue is present. Specifically, if a boy has nonpalpable testicles, hormones such as human chorionic gonadotropin (hCG) are administered to stimulate the testicles. Increased levels of testosterone after administration of hCG suggest that there is at least one viable testicle somewhere in the body, while no hormone response suggests anorchia. The theoretical basis for using hormone stimulation to guide treatment is that, if there is no testicle present at all, then surgery is unnecessary and a child may be able to be spared the risks of exploratory surgery to find a missing testicle.

Imaging also is used to determine whether there is in fact a testicle and, if there is, to locate it in order to guide the optimal treatment approach. Imaging approaches include ultrasonography (US), computerized tomography (CT) scanning, routine magnetic resonance imaging (MRI), and magnetic resonance (MR) angiography and venography, some of which require sedation or anesthesia and are thus not without risks.

Medical options in the treatment of cryptorchidism consist of hormones intended to increase circulating androgens. This increase in circulating androgens, in turn, is thought to potentially promote testicular descent. The two hormones that are most commonly used for the treatment of cryptorchidism are luteinizing hormone-releasing hormone (abbreviated as LHRH and also sometimes referred to as gonadotropin-releasing hormone [GnRH]) and hCG. Although used much less commonly, human menopausal gonadotropin (hMG) also is used occasionally and is thought to function in a manner similar to hCG. LHRH and its analogs and agonists can be administered intranasally, while hCG and hMG must be injected intramuscularly.

There are three primary surgical options for orchiopexy (surgery to move an undescended testicle into the scrotum), depending on the location and appearance of the undescended testicle. Primary orchiopexy is possible if the testicle is of normal size and appearance and if the testicular vessels are of adequate length. In this procedure, the testicle is surgically moved to the scrotum and fixed in place. Primary orchiopexy requires that the vessels be long enough to reach into the scrotum. If the vessels are so short that tension-free placement of the testicle in the scrotum is not possible, a Fowler-Stephens (FS) orchiopexy is performed. This procedure entails ligating the testicular vessels. The testicular blood supply then depends on collateral circulation from the deferential artery and the cremasteric system.[1]

The FS technique can take place in one of two ways: either (1) as a single-stage operation, in which the vessels are ligated and the testicle is then placed into the proper position in the scrotum, or (2) as a two-stage procedure, in which the vessels are ligated in the first operation, the testicle is allowed to develop presumably better collateral circulation in its abdominal position, and it is then moved to the proper position in the scrotum during a second procedure, usually 3–6 months later. Both primary orchiopexy and the FS procedure can be performed using laparoscopic or open surgical technique.

Finally, surgical orchiectomy (removal of the testicle) also can be performed, although this is usually reserved for cases where the testicle is not felt to be viable, as the primary goal of treatment is relocation of a viable testicle to a dependent position in the scrotum. Orchiectomy is not reviewed in this report, which focuses only on procedures to maintain testicular tissue and viability.

Clinical uncertainty and lack of guidance exist on the appropriate clinical pathway for treatment of cryptorchidism. Areas of uncertainty include selecting the optimal approach to treatment planning (imaging vs. no imaging, hormonal stimulation testing or not) and intervention (surgical vs. hormonal, one-stage vs. two-stage FS, various modifications of each of the surgical techniques, and open vs. laparoscopic approach). The immediate goal of most interventions for cryptorchidism is to reposition the undescended gonad in a "normal" position in the scrotum. Intermediate outcomes include psychological benefits in terms of body image, and long-term goals include preservation of fertility and prevention

of testicular malignancy. All of these outcomes are important to patients.

## Scope

This review focuses on the effectiveness of imaging for identifying and correctly locating testicles, on the use of hormonal stimulation for identifying anorchia in treatment planning, on hormones for achieving testicular descent, and on choices among surgical treatments, including surgical approach (open vs. laparoscopic).

### Key Questions

We have synthesized evidence in the published literature to address the following Key Questions (KQs) and population, interventions, comparators, outcomes, timing, and settings (PICOTS).

**KQ1a.** For determining a course of treatment, is imaging equivalent to laparoscopy in determining the presence and location of a nonpalpable testicle?

**KQ1b.** In male children with bilateral nonpalpable testicles, does the use of hormonal stimulation testing reduce the need for surgery as part of a treatment plan?

**KQ2.** What is the effectiveness of initial hormonal therapy (human chorionic gonadotropin or luteinizing hormone-releasing hormone) for the treatment of cryptorchidism for outcomes, including but not limited to:

- Further surgical intervention
- The effect on infertility/subfertility
- The development of testicular malignancy
- The size, location, and function of the testicles

**KQ3.** What is the effectiveness of surgical therapies (one-stage vs. two-stage, laparoscopic vs. open approach) for the treatment of cryptorchidism for outcomes, including but not limited to:

- Further surgical intervention
- The effect on infertility/subfertility
- The development of testicular malignancy
- The size, location, and function of the testicles

**KQ4.** How do the age at presentation, physical presentation of cryptorchidism (unilateral vs. bilateral, palpable vs. nonpalpable, anatomic location), and occurrence of associated abnormalities (e.g., hernia) modify diagnosis, treatment, and outcomes?

**KQ5.** What are the nature and frequency of harms associated with workup or treatment for cryptorchidism?

## Methods

### Literature Search Strategy

We searched the following databases: MEDLINE® via the PubMed interface, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Embase. Details of the search strategy are available in the full report. The search strategy excluded studies not relevant to human populations and those that were not published in English. Based on input from the Technical Expert Panel and awareness of advances in surgical technique, including development of imaging techniques, we also excluded studies published before 1980. We required that study participants be prepubescent boys with cryptorchidism. For KQ1a and KQ1b, we accepted single-arm studies because the purpose of those questions was to assess treatment planning, which is based on the success of the approaches for identifying and locating testicles before and after surgical confirmation. For the treatment questions (KQ2 and KQ3), however, studies had to include an appropriate comparison group (i.e., comparison of different treatments, hormonal vs. surgical therapy, or treatment vs. no treatment). Studies of individuals with disorders of sexual development or ambiguous genitalia were excluded, because the clinical complexity of these patients means that they typically undergo multiple treatments for their conditions and results in this population would not be generalizable to the population typically presenting with cryptorchidism. In addition, for KQ1a we included only studies that evaluated the accuracy with which preoperative imaging techniques identified the presence and location of testicles, with confirmation by surgery. If a study had negative imaging for all subjects, if the imaging techniques were not adequately described, or if relevant data to calculate diagnostic performance were not available, it was excluded. We required that the study report data on presence or absence of testicles along with identifying the position of testicles (abdominal, inguinal, or scrotal) as determined by imaging techniques and surgery.

Data were extracted into evidence tables for qualitative synthesis. All data extraction was done by an investigator on the team and verified by a second investigator. The data extracted included information on the study design, participant population, baseline and followup data on testicular position and other outcomes that were available, and harms experienced in the study.

### Quality Assessment of Individual Studies

Quality was assessed using three published tools, depending on the study design. Two reviewers independently assessed the quality of each study, and then results were adjudicated. For randomized controlled trials (RCTs), we used the Cochrane Risk of Bias tool;[6] for cohort studies, the Newcastle-Ottawa Quality Assessment Scale;[7] and for prognostic studies of imaging, the Quality Assessment of Diagnostic Accuracy Studies-Revised (QUADAS-2) tool.[8] The results of these tools were then translated to the Agency for Healthcare Research and Quality standard of "good," "fair," and "poor" quality designations using conversion thresholds developed by the team, as no explicit guidance exists. The conversion thresholds are presented in the main report.

### Data Synthesis

Evidence tables were completed for all included studies, and data are presented in summary tables and analyzed qualitatively in the text. In addition, quantitative analysis was used for KQ1a (imaging compared with laparoscopy) and KQ3 (surgical therapies).

For KQ1a, the accuracy of imaging techniques was calculated for concordance with surgical results (open or laparoscopic), which were considered the gold standard. The performance characteristic data for each imaging technique compared with surgery was calculated, as was an overall accuracy rate. The ability of each imaging modality to correctly classify the position of the testicles also was calculated using the following categories, which refer to the location of the cryptorchid testicle: intra-abdominal (in the abdomen), inguino-scrotal (in the groin area or too high in the scrotum), or atrophied.

For KQ3, data on success of testicular descent were pooled and the weighted proportions (sum of all successfully treated testicles/total number of testicles in studies) were calculated for each treatment type. Similarly, weighted testicular atrophy rates were derived for each of the surgical techniques.

### Strength of the Body of Evidence

We assessed the strength of the evidence for the main comparisons within the two primary treatment approaches (hormonal treatment and surgery) for the primary outcomes of testicular descent and atrophy. We used the approach to strength of evidence assessment described in the Effective Health Care Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[8]

We examined the following four major domains:

- Risk of bias (low, medium, or high)
- Consistency of findings (inconsistency not present, inconsistency present, or unknown or not applicable)
- Directness (direct comparison of influence on outcomes in RCT or indirect information from observational research)
- Precision (precise or imprecise based on outcome rates, size of the individual studies, and the total number of participants in the studies for the category of intervention)

The overall strength of evidence could be graded as "high" (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect).

### Applicability

The degree to which the findings in the review are likely to be applicable to clinical practice was assessed using a PICOTS framework according to the applicability chapter of the Methods Guide of the Effective Health Care Program.[9]

## Results

We identified 3,448 nonduplicate titles or abstracts with potential relevance through the search process, with 830 proceeding to full-text review. Sixty-four, representing 60 distinct studies, were included in the review: 16 RCTs (2 good quality, 2 fair quality, 12 poor quality); 5 prospective cohort studies (1 good quality, 2 fair quality, 2 poor quality); 21 retrospective cohort studies (4 good quality, 17 poor quality); 16 prospective case series (1 good quality, 3 fair quality, 12 poor quality); and 2 retrospective case series (1 fair quality and 1 poor quality). Eighteen studies pertain to KQ1a, 2 studies to KQ1b, 14 studies to KQ2, 26 studies to KQ3, 23 studies to KQ4, and 11 studies to KQ5. See the full report for references to each study.

### KQ1a. Utility of Imaging To Determine Course of Treatment

Eighteen unique studies met our inclusion criteria and addressed the performance of imaging techniques in identifying and localizing nonpalpable undescended testicles in prepubescent boys. Only four studies adequately described selection criteria for the participants, and three studies provided the time interval between imaging techniques and surgery. One study was of good quality, 4 of fair quality, and 13 of poor quality. More studies were conducted in Asia (N=9) than in the United States (N=4) or Europe (N=5). All of the studies were conducted in a hospital setting. The number of participants in the studies ranged from 11 to 135. The potential number of nonpalpable testicles to be localized ranged from 11 to 152. The boys' ages were between 1 month and 18 years.

Using surgery as a reference standard, the overall accuracy rate at identifying testicles using US ranged from 21 to 76 percent across the studies, compared with 42 to 92 percent for MRI and 60 percent in the one study on CT scan. The one good-quality study of US had an accuracy rate of 73 percent. Both magnetic resonance angiogram (MRA) and magnetic resonance venography (MRV) had 100-percent accuracy, but MRA was assessed in only two studies and MRV in one. There were no good-quality studies of MRA/MRV. Both techniques require anesthesia or sedation.

The accuracy of imaging techniques depended on the actual location of the testicles or whether they were atrophied. Neither US nor MRI demonstrated high accuracy at identifying atrophied testicles (16.7% and 32.3%, respectively), compared with 100-percent accuracy for MRA and MRV. When the testicles were located in the inguino-scrotal area, however, US demonstrated a 92-percent accuracy rate, compared with 83-percent accuracy for MRI. Performance was worse when the testicles were located intra-abdominally, with US demonstrating 33.7-percent accuracy and MRI 71.2-percent accuracy.

### KQ1b. Utility of Hormone Stimulation Testing To Determine Course of Treatment

Two studies of a total of 44 boys examined the potential for hormonal stimulation testing to predict anorchia. One had fair quality and one had poor quality. Both were cohort studies in which hCG was used to stimulate testosterone secretion in order to diagnose any impairment in testicular endocrine function. Both used a similar study design, in which the participant was first given hCG to stimulate testosterone production and then underwent surgical exploration to confirm the absence or presence of viable testicular tissue.

Both studies reported 100-percent sensitivity, indicating that no nonviable testicles were missed. However, the studies were small and lacked a proper comparison of test characteristics between the two thresholds assessed (a greater than twofold increase in serum testosterone levels or a total testosterone of >5 ng/mmol after stimulation).

### KQ2. Effectiveness of Hormone Therapy

Fourteen studies in 19 publications assessed hormonal therapy in treatment. Individual studies often included multiple arms. Six studies compared LHRH with placebo, one compared hCG with placebo, four compared LHRH with hCG, and six compared various doses or regimens. Of the 14 studies, 11 were RCTs, two were prospective cohort studies, and one was a retrospective cohort study. Three studies were of good quality, two were of fair quality, and nine were of poor quality.

Six studies specifically compared successful testicular descent rates following administration of either LHRH or placebo in boys with cryptorchidism (two fair quality and four poor quality). Four of five two-arm studies concluded that LHRH was more effective than placebo in inducing testicular descent, with variable reported effect sizes across studies (Table A). No harms of hormonal treatment were reported.

LHRH was compared with hCG and placebo in one study of fair quality. In that three-arm study, results comparing LHRH with placebo were equivocal, with LHRH being more effective than placebo in achieving testicular descent in patients with bilateral cryptorchidism, but being no better than placebo in patients with unilateral cryptorchidism. In this same study, hCG was better than placebo at achieving testicular descent in both bilateral and unilateral patients, but with only this one study of fair quality, the strength of evidence is insufficient. Four studies provided data on LHRH compared with hCG, with no clear indication of either being better than the other. The studies that compared doses and dosing schedules within hormone type were of poor quality and too heterogeneous to permit drawing useful conclusions.

Initial location of the testicle may influence success rates, but no study was adequately powered to assess this possibility. Studies of hCG have reported more frequent temporary virilizing side effects than those seen with LHRH or placebo, including increased penile length, erections, and testicular enlargement. All side effects were transitory.

**Table A. Short-term testicular descent in two-arm, randomized, placebo-controlled studies**

| Study<br>N<br>Length of Followup<br>Quality | LHRH Dose | LHRH Frequency | LHRH Duration | LHRH Descent (%) | Placebo Descent (%) |
|---|---|---|---|---|---|
| Olsen et al., 1992<br>N = 123<br>4 weeks<br>Fair | 400 µg | 3 times daily | 4 weeks | 9.7 | 1.6[a] |
| De Muinck Keizer-Schrama et al. and Hazebroek et al., 1986-87<br>N = 237<br>8 weeks<br>Poor | 200 µg | 3 times daily | 4 weeks | 9.0 | 8.0 |
| Hagberg and Westphal, 1982<br>N = 50<br>4 weeks<br>Poor | 100 µg | 3 times daily | 28 days | 62.0 | 3.0 |
| Karpe et al., 1983<br>N = 50<br>6 months<br>Poor | 100 µg | 6 times daily | 28 days | 20.0 | 12.0 |
| Wit et al., 1986<br>N = 49<br>8 weeks<br>Poor | 400 µg | 3 times daily | 28 days | 37 | 18 |

CI = confidence interval; LHRH = luteinizing hormone-releasing hormone
[a]Statistical significance was reported only for this comparison—p=0.12 (95% CI, 0.1 to 16.6).

### KQ3. Effectiveness of Surgical Treatments

Twenty-six studies addressed surgical treatment. Four studies were judged to be of good quality, one of fair quality, and the remainder of poor quality. Eleven studies reported outcomes following either one-stage FS orchiopexy, two-stage FS orchiopexy, or primary orchiopexy. Five studies compared an open versus laparoscopic approach for the same procedure (one good quality, one fair, and three poor quality). Six studies compared minor surgical variations of primary orchiopexy (one good quality, five poor quality).

Three poor-quality studies reported long-term fertility outcomes in men who had undergone various surgical procedures for cryptorchidism in childhood. One good-quality study compared endocrine function in children with surgically treated or untreated cryptorchidism.

Surgical treatment for cryptorchidism was associated with success rates of testicular descent that ranged from 33 percent to 100 percent (Tables B–D), depending on type of surgery, with type of surgery depending on clinical presentation. No studies compared hormonal therapy alone to surgery. Only one study assessing testicular descent was rated as good quality. This study had a testicular descent rate of 63 percent for one-stage FS, 67.6 percent for two-stage FS, and 89.1 percent for primary orchiopexy, slightly lower in all types of surgery than the pooled estimate.

The weighted success rate for all three approaches exceeds 75 percent. The overall success rate for one-stage FS is 78.7 percent (Table B). The overall success rate for two-stage FS is 86 percent (Table C).

The overall success rate of primary orchiopexy is 96.4 percent (Table D). Each type of surgery is used to address a different clinical presentation, so these success rates are not intended to be compared with one another.

The use of laparoscopy has increased across all surgical fields in the last decade. Laparoscopy in the treatment of cryptorchidism has two roles: (1) as an exploratory tool to locate a nonpalpable undescended testicle in the abdomen and (2) as a minimally invasive method of orchiopexy. Two studies assessed laparoscopy for determining the

| Table B. Success rates after one-stage Fowler-Stephens | | | | |
|---|---|---|---|---|
| **Study Country** | **Quality** | **Total Participants** | **Total Testicles** | **% Success (N Testicles)** |
| Stec et al., 2009 United States | Good | 136 | 156 | 63 (27) |
| Baker et al., 2001 United States | Poor | 226 | 263 | 74.1 (27) |
| Chang et al., 2001 United States | Poor | 80 | 92 | 84 (19) |
| Chang et al., 2008 United States | Poor | 48 | 48 | 94.3 (35) |
| Comploj et al., 2011 Austria | Poor | 41 | 50 | 79 (33) |
| Denes et al., 2008 Brazil | Poor | 46 | 54 | 33 (3) |
| Kim et al., 2010[a] South Korea | Poor | 67 | 86 | 82 (11) |
| Total | NA | 644 | 749 | 78.7[b] |

NA = not applicable
[a]Controlled for location.
[b]Pooled percent.
Note: All studies were retrospective cohorts.

| Table C. Success rates after two-stage Fowler-Stephens | | | | |
|---|---|---|---|---|
| **Study Country** | **Quality** | **Total Participants** | **Total Testicles** | **% Success (N Testicles)** |
| Stec et al., 2009 United States | Good | 136 | 156 | 67.6 (37) |
| Baker et al., 2001 United States | Poor | 226 | 263 | 87.9 (58) |
| Chang et al., 2001 United States | Poor | 80 | 92 | 86 (7) |
| Chang et al., 2008 United States | Poor | 48 | 48 | 80 (10) |
| Comploj et al., 2011 Austria | Poor | 41 | 50 | 82 (17) |
| Denes et al., 2008 Brazil | Poor | 46 | 54 | 88 (25) |
| Dhanani et al., 2004 United States | Poor | 74 | 83 | 98 (49) |
| Kim et al., 2010[a] South Korea | Poor | 67 | 86 | 67 (3) |
| Moursy et al., 2011 Egypt | Poor | 66 | 76 | 88.8 (36) |
| Total | NA | 784 | 908 | 86.0[b] |

NA = not applicable
[a]Controlled for location.
[b]Pooled percent.
Note: All studies were retrospective cohorts.

| Table D. Success rates after primary orchiopexy | | | | |
|---|---|---|---|---|
| **Study Country** | **Quality** | **Total Participants** | **Total Testicles** | **% Success (N Testicles)** |
| Stec et al., 2009 United States | Good | 136 | 156 | 89.1 (92) |
| Baker et al., 2001 United States | Poor | 226 | 263 | 97.2 (178) |
| Chang et al., 2001 United States | Poor | 80 | 92 | 100 (66) |
| Denes et al., 2008 Brazil | Poor | 46 | 54 | 96 (26) |
| Dhanani et al., 2004 United States | Poor | 74 | 83 | 100 (28) |
| Kim et al., 2010[a] South Korea | Poor | 67 | 86 | 98 (49) |
| Moursy et al., 2011 Egypt | Poor | 66 | 76 | 100 (28) |
| Total | NA | 695 | 810 | 96.4[b] |

NA = not applicable
[a]Controlled for location.
[b]Pooled percent.
Note: All studies were retrospective cohorts.

location of the testicle and reported that it performed similarly to open exploration. Success of the ensuing surgeries was also similar, regardless of exploratory approach. Neither study addressed postoperative pain or time to return to normal activity. Neither study included a clinically relevant outcome, so we did not assess the strength of the evidence for this comparison.

Notably, all but one of the studies in our review published in the past 5 years that included assessment of the abdomen for a nonpalpable testicle used laparoscopy for this part of the procedure, even if they used an open technique to repair the cryptorchidism. This suggests that the results of the two studies comparing laparoscopic with open approaches are applicable to current practice.

One fair-quality and two poor-quality studies compared the use of a laparoscopic approach with open surgery for performance of orchiopexy. They reported similar clinical outcomes and less pain, shorter hospital stays, and a quicker return to normal activity with laparoscopy. No studies reported on the surgical learning curve, which is a potential modifier of effectiveness.

Few studies compared the effectiveness of different interventions associated with treatment for cryptorchidism on future fertility. Furthermore, in those studies (in which the participants are adults who had cryptorchidism in childhood), the primary outcome is usually semen analysis parameters, which are at best a proxy for fertility. One study examined ability to father children and focused on the addition of hormonal therapy to surgery; it found no advantage to the combination of hormones and surgery compared with surgery alone. No studies compared paternity rates between surgery and hormonal therapy in isolation. Therefore, no data are available to assess whether one approach is superior for fertility outcomes, although it is accepted that untreated cryptorchidism is associated negatively with later fertility.

### KQ4. Modifiers of Treatment

Twenty-three studies reported modifier data, including 18 imaging studies (1 good quality, 3 fair, and 14 poor quality) and 3 studies of hormonal treatment (1 good quality and 2 poor quality). It has been suggested that in studies of hormonal treatment, age of the patient and initial position of the testicle affect outcomes. However, the reporting of data by age was inconsistent in two poor-quality studies (reported in four publications). Specifically, these two studies include patients with a wide range of ages, starting at birth and progressing through puberty. In addition, the two studies categorize age differently, making it impossible to consolidate the two studies and draw

conclusions regarding the relationship between age and outcomes.

Most studies that provided data on pretreatment testicular position did not provide outcomes stratified on this measure, but those that did reported higher rates of descent if the testicle was initially lower. In one poor-quality study of LHRH that assessed the role of testicular position, 75 percent of testicles that descended could be manipulated at least to the scrotal entrance before treatment. A second poor-quality study, of hCG, reported success rates 2 to 3 times as high for initially inguinal testicles compared with those located intra-abdominally. Across the studies, the degree to which these lower testicles included in success rates are, in fact, retractile is unclear.

In one good-quality study of surgical repair specifically intended to examine factors associated with success, a retrospective review was performed of orchiopexies performed over 9 years at one institution. Multivariate analysis demonstrated that neither age nor patent processus vaginalis modified outcomes.

### KQ5. Harms of Workup or Treatment

Eleven studies of hormonal and surgical interventions included harms. Two studies were of good quality, two were of fair quality, and seven were of poor quality. Theoretically, harms of imaging could include exposure to radiation or to contrast, but data on harms were not provided in any imaging studies included in the review. Reported harms of hormonal treatments were mild and transient. The most common outcomes were virilizing effects (e.g., hair, increase in penis size, and erections) and behavioral changes (e.g., aggression). In all studies, reported harms had receded by 6-month followup, if not before.

Rare cases of intestinal injury due to Veress needle puncture (one case) and to postoperative laparoscopic port site reducible hernia (three cases) and incarcerated hernia (two cases) were noted with laparoscopy. These adverse events are associated with the use of the laparoscopic approach and are not unexpected in this setting. They are not specific to cryptorchidism repair and can occur with any type of laparoscopy. Overall, adverse effects specifically associated with surgical repair for cryptorchidism were rare.

## Discussion

### Key Findings and Strength of Evidence

The goal of an intervention for cryptorchidism is to move the undescended testicle to a normal position in the scrotum in the safest and least invasive way possible. This report reviews the literature on treatment planning and therapeutic interventions to achieve these goals. Overall, only eight good-quality studies were available for analysis, and this lack of good-quality studies is reflected in the strength of evidence, which was generally low to moderate for any intervention and outcome. Strength of evidence was high only for the effect of primary orchiopexy on testicular descent, for which the most data are available.

Imaging approaches have a range of success rates at localizing cryptorchid testicles from 21 to 100 percent. The imaging literature provides mixed results for identifying cases of anorchia, with studies not pointing to a particular approach that provides adequate accuracy at identifying atrophy or complete absence of the testicle and thus could be used to avoid surgical intervention. The lack of good-quality studies affects our degree of confidence in establishing a rate of prediction of anorchia, but results do not seem to be directly related to study quality. Applicability of the results on imaging depends on access and acceptability of the imaging approaches. Imaging approaches range from being readily available in the case of US to potentially less available for the approaches using MR. Some approaches require sedation, and reported success rates may reflect, in part, differences in the patient selection process, number of participants in each study, and the type of testicles present. Information on full physical exam, including obesity, condition of contralateral testicles, and prior hormonal or surgical treatment, which may all play a role in the performance of imaging, also was lacking. Only two studies (one fair quality and one poor) of hormonal stimulation testing for identifying viable testicular tissue were available, and more study is needed in this area. Most studies of hormonal treatment were of poor quality, precluding definitive conclusions as to a specific expected effect rate for any hormone or combination thereof. Nonetheless, studies report slightly higher rates of testicular descent for LHRH and hCG compared with placebo. End users of this report will need to balance this information with difficulties of administration in young children and potential side effects. Initial location of the testicle may influence success rates. Although no study was adequately powered to assess this possibility, most studies that provide the data indicate higher success rates for testicles initially lower in position. Some studies have reported more frequent temporary virilizing side effects, including increased penile length, erections, and testicular enlargement, but all side effects were transitory.

We assessed the strength of evidence for our primary outcome of testicular descent (Table E). There is moderate

**Table E. Strength of evidence on testicular descent with hormonal treatments for cryptorchidism**

| Treatment Comparison Number of Studies; Total Subjects; Testes Treated | Study Design/ Risk of Bias | Consistency | Directness | Precision | Strength of Evidence and Magnitude of Effect |
|---|---|---|---|---|---|
| **LHRH vs. placebo 6; 752; 935** | RCT/ Moderate | Consistent | Direct | Imprecise | Moderate LHRH: 9%–62% Placebo: 0%–18% |
| **hCG vs. placebo 1; 243; 280** | RCT/ Moderate | Unknown | Direct | Unknown | Low Bilateral: 23% vs. 0% Unilateral: 15% vs. 0% |
| **LHRH vs. hCG 3; 431; 465** | RCT/ Low | Inconsistent | Direct | Imprecise | Low LHRH: 0%–18.8% hCG: 5.9%–23% |
| **LHRH vs. hCG 1; 324; 198** | Cohort/ High | Consistent | Direct | Imprecise | Low LHRH: 29.4% hCG: 34.5% |

hCG = human chorionic gonadotropin; LHRH = luteinizing hormone-releasing hormone; RCT = randomized controlled trial

strength of evidence for increased testicular descent with LHRH compared with placebo, low strength of evidence for increased testicular descent with hCG compared with placebo, and low strength of evidence for equivalence between LHRH and hCG.

No studies provided cancer or fertility outcomes for the comparisons listed, so the strength of evidence is insufficient for these outcomes. Each surgical approach was assessed independently for ability to achieve testicular descent because, as described in the report, each approach is used under different clinical circumstances, and thus it is inappropriate to compare them with one another. We assessed the strength of evidence as our confidence in the weighted average of successful testicular descent associated with each surgical approach separately (Table F). Although retrospective studies typically have high risk of bias because of lack of a control group, in grading the overall strength of the evidence, we used an implicit comparator group, given the known natural history of disease. Given the low rate of spontaneous testicular descent, despite the high risk of bias of retrospective studies, strength of evidence might be considered high because of the high magnitude of effect when compared with an implicit control.

For the outcome of testicular descent, strength of evidence was moderate for one- and two-stage orchiopexy and high for primary orchiopexy. All studies were retrospective cohort studies and thus had high risk of bias, but we deemed this to be an appropriate study design for the question of the ability of orchiopexy to achieve testicular descent, and we considered the relative challenges of this design to be outweighed by the magnitude of effect. Primary orchiopexy had higher strength of evidence than one-stage and two-stage procedures based on the higher number of testicles (outcomes) reported in the literature.

We also assessed strength of evidence for the outcome of testicular atrophy, and on the same methodologic basis as was used for testicular descent, found the strength of evidence to be low for a 28.1-percent atrophy rate with one-stage FS, low for an 8.2-percent atrophy rate with two-stage FS, and moderate for a 1.83-percent atrophy rate for primary orchiopexy.

We assessed the strength of evidence for equivalence of laparoscopic and open approaches for achieving testicular descent to be low, with only one RCT of poor quality and two cohort studies of fair and poor quality, although the individual studies report that success rates are similar with both approaches. Similarly, strength of evidence was low for the effect of the approach on atrophy.

### Contextual Information Not Covered in the Review

Although the comparative literature does not include long-term data on either fertility or cancer outcomes, there is a

| Table F. Strength of evidence of surgical treatments for cryptorchidism | | | | | |
|---|---|---|---|---|---|
| **Outcome Treatment Number of Studies; Total Subjects; Treated Testicles** | **Study Design/ Risk of Bias** | **Consistency** | **Directness** | **Precision** | **Strength of Evidence and Magnitude of Effect[a]** |
| **Testicular Descent** | | | | | |
| **1-stage FS 7; 644; 155** | Retrospective cohort/ High | Consistent | Direct | Imprecise | Moderate 78.7% (range: 33%–94.3%) |
| **2-stage FS 9; 784; 242** | Retrospective cohort/ High | Consistent | Direct | Imprecise | Moderate 86.0% (range: 67%–98%) |
| **Primary orchiopexy 7; 695; 467** | Retrospective cohort/ High | Consistent | Direct | Precise | High 96.4% (range: 89.1%–100%) |
| **Atrophy** | | | | | |
| **1-stage FS 3; 320;32** | Retrospective cohort/ High | Consistent | Direct | Imprecise | Low 28.1% (range: 22%–67%) |
| **2-stage FS 5; 470; 158** | Retrospective cohort/ High | Consistent | Direct | Precise | Low 8.2% (range: 0%–12%) |
| **Primary orchiopexy 5; 470; 273** | Retrospective cohort/ High | Consistent | Direct | Precise | Moderate 1.83% (range: 0%–4%) |

FS = Fowler-Stephens
[a]Pooled proportion (range).

body of epidemiologic data and data from noncomparative studies to which we refer end users of this report. These studies did not meet the specific scope or inclusion criteria for our review, but they provide important information on long-term outcomes for individuals with cryptorchidism. Because we did not review these studies systematically as part of the scope of this review, we do not suggest that the references included here are comprehensive; rather they are representative and provide additional context for decisionmakers. Of particular note is a series of studies by Peter Lee and colleagues that describe long-term outcomes, including the ability to father children, among men treated surgically for cryptorchidism who have attempted paternity. These studies suggest that while men who were treated for unilateral cryptorchidism as children do not have substantially lower paternity rates than control subjects, men treated for bilateral cryptorchidism experience substantially lower paternity than both those with previous unilateral cryptorchidism and controls. These studies do not include untreated individuals with cryptorchidism; rather, the cryptorchid groups are "previously cryptorchid," having undergone surgery.

## Applicability

The degree to which the data presented in this report are applicable to clinical care depends on the degree to which the population included in the studies represents the patient population in clinical care, as well as the availability of the interventions and the degree to which the study settings mirror those in usual clinical practice. Across all KQs, there is no indication that study populations are different from those in standard clinical practice. Indeed, many of the studies included are reports of clinical practice, including chart reviews. Study populations included children with undescended testicles, as required by our inclusion criteria. Data are provided across the studies on children with a range of initial testicular locations (e.g., intra-abdominal, inguinal, or scrotal) and unilateral or bilateral disease. The applicability of the imaging results depends on the availability of the specific imaging technologies in a given clinical setting, including the availability of trained and experienced operators. The applicability of the imaging results may also depend on patient age, with technologies requiring patient

cooperation potentially more challenging to use in infants. With improvements in imaging techniques, it may also be the case that early studies underestimated the effectiveness of imaging technologies.

Hormonal approaches to treatment were assessed in children with both bilateral and unilateral cryptorchidism and at varying ages, providing data for the range of patients likely to be seen in clinical practice in the United States. Although most studies took place in Europe, the results should be applicable to a U.S. population, as the hormonal agents are readily available in the United States.

As with the hormonal treatment literature, the surgical literature applies to the range of patients likely to be seen in practice, and the surgical techniques assessed are those commonly used in U.S. clinical care. The most common outcome assessed was testicular position; this is typically the outcome targeted in clinical practice. In addition, most studies provided adequate followup data to assess later atrophy.

### Research Gaps

Although a number of studies are available on US and MR approaches, very few studies are available on MRA and MRV, which could be useful for confirming findings after negative US and MRI. A study comparing multiple imaging modalities, such as US or MR, in the same patient, followed by diagnostic laparoscopy and appropriate treatment, would be of value in assessing the equivalence or superiority of any imaging approach.

Studies of hormonal treatment of cryptorchidism have focused primarily on LHRH and its agonists because it is easily administered intranasally. The wide range of success rates seen across studies is possibly due to heterogeneity in the study populations or potentially due to variability in drug absorption through the intranasal route. Some literature suggests that differences may be due to initial location of the testicle, but this is an area warranting more study, including conducting additional studies in which patients are carefully selected to assess efficacy by testicle location or analyses carefully controlled for this effect. Any side effects from hormonal therapy are temporary and not life threatening. It would be of some value to be able to accurately inform parents of the possibility of success with this treatment, as even a small likelihood of success coupled with avoidance of surgery may be appealing.

Current literature lacks assessment of whether a one-stage or two-stage method for the FS approach to surgery is superior or whether the two methods are similar. An appropriately designed RCT is needed of one-stage versus two-stage FS in children with nonpalpable, presumably intra-abdominal testicles, who are determined not to be candidates for primary orchiopexy. In order for this comparison to be valid, the trial would also need to control for location within the abdomen at the time of presentation in order to avoid the shortfalls of the current observational literature. The primary outcome should be successful placement of a normal-sized testicle in the dependent portion of the scrotum. Ideally, outcomes would be measured both immediately and in the longer term (6 to 12 months later) to assess late complications, recurrences, and atrophy. Such a trial would be ethical, as primary orchiopexy would not be the focus of the study and would not be denied to patients in whom it could be performed.

The appropriate age for treatment remains unknown, with very little data available on the modifying effect of age on outcomes. Across all approaches to treatment planning and therapy, this important question has yet to be answered. Studies of long-term outcomes of treatment, both fertility and cancer, are notably missing. Development of a long-term cohort or a registry could provide broader and longer term data, and warrants consideration. When studies are published on fertility outcomes, the specific measures are inadequate, as they focus only on semen analysis (normal: >15 sperm per millimeter, >50 percent having normal motility and >4 percent having normal morphology). More appropriate measures should be included, such as the ability to achieve paternity when desired. Additional outcomes that warrant study are good measures of endocrine function, which is assessed by serum testosterone levels. (Normal values vary by patient age and laboratory but are generally 10–44 nmol/l.)

### Conclusions

No specific imaging technique is able to completely identify anorchia or descent of the testicles and thus eliminate the need for further surgical evaluation. Accuracy varies by location of the testicles, with less invasive methods (9 studies of US, including 1 good, 2 fair, and 6 poor quality; 10 studies of MRI, including 3 fair and 7 poor quality) demonstrating poor accuracy for abdominally located testicles and those that are atrophied. Hormonal stimulation testing may predict anorchia, but more research is needed, with only two studies (one fair and one poor quality) of fewer than 50 participants. Hormonal treatment is somewhat more effective relative to placebo, with moderate strength of evidence, and is successful in some children with minimal side effects. Surgical options are effective, with rates of normal postoperative scrotal position above 75 percent. The

strength of the evidence is moderate (low for atrophy) for the effects of either one-stage or two-stage FS procedures on testicular descent and high (moderate for atrophy) for primary orchiopexy. Comparable outcomes have been seen with laparoscopic and open approaches to surgical repair, with low strength of evidence overall.

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## Full Report

This executive summary is part of the following document: Penson DF, Krishnaswami S, Jules A, Seroogy JC, McPheeters ML. Evaluation and Treatment of Cryptorchidism. Comparative Effectiveness Review No. 88. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 13-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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AHRQ Pub. No. 13-EHC001-1
December 2012