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Effectiveness of Hormonal and Surgical Therapies for Cryptorchidism: A Systematic Review

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KEY WORDS

cryptorchidism, undescended testicle, systematic review

ABBREVIATIONS

FS—Fowler-Stephens procedure

hCG—human chorionic gonadotropin

LHRH—luteinizing hormone releasing hormone

RCT—randomized controlled trial

SOE—strength of evidence

All authors helped to conceptualize the study, extract and analyze data, draft the manuscript, revise it critically for important intellectual content, and gave final approval of the manuscript submitted.

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abstract

BACKGROUND AND OBJECTIVE: Controversy remains concerning the optimal treatment approach for cryptorchidism. The objective of this study was to assess effectiveness of hormone therapy or surgery for cryptorchidism.

METHODS: We searched Medline and other databases from 1980 to February 2012. Two reviewers independently assessed studies against predetermined criteria. Two reviewers independently extracted data and assigned overall quality and strength of evidence ratings using predetermined criteria.

RESULTS: Fourteen studies addressed effectiveness of hormonal treatments, and 26 studies addressed surgical intervention outcomes. Hormonal treatment is associated with testicular descent in some children, but rates generally do not exceed those seen with placebo by >10%. Surgical treatment is associated with success rates of testicular descent ranging from 33% to 100%, depending on surgery. Weighted success averages were 78.7% for 1-stage Fowler-Stephens (FS), 86% for 2-stage FS, and 96.4% for primary orchiopexy. Descent rates were similar among studies comparing laparoscopic and open surgeries. Reported harms of hormonal treatments were mild and transient. Adverse effects specifically associated with surgical repair were rare.

CONCLUSIONS: The body of the reviewed literature comprises primarily fair- and poor-quality studies, limiting our ability to draw definitive conclusions. Hormonal treatment is marginally effective relative to placebo but is successful in some children and with minimal harms, suggesting that it may be an appropriate trial of care for some patients. Surgical options are effective, with high rates of testicular descent (moderate strength of evidence for FS procedures, high for primary orchiopexy). Comparable outcomes occur with laparoscopic and open approaches. *Pediatrics* 2013;131:e1897–e1907

Cryptorchidism is a congenital condition in which 1 or both testicles are not appropriately positioned in the scrotum at birth and cannot be moved into the proper position manually. It affects an estimated 3% of full-term male neonates and up to 30% of premature infants, making it the most common male genital anomaly identified at birth.^{1,2} Although about 70% of cryptorchid testicles spontaneously descend within the first year of life (most occurring in the first 3 months), the number of boys whose condition persists remains constant at ~1%.^{1,2} Longer-term consequences of cryptorchidism can include testicular malignancy and infertility/subfertility. Once cryptorchidism is diagnosed, treatment choices may include watchful waiting, hormonal treatment, or surgery.

In clinical practice, the choice of initial therapy is often selected on the basis of age at presentation and the location of the cryptorchid testicle.^{3,4} Watchful waiting may be used in boys <1 year of age with lower-lying testis in whom spontaneous descent is still a realistic possibility. Hormonal and surgical options are primarily selected on the basis of location and appearance of the undescended testicle. Hormonal treatment with luteinizing hormone releasing hormone (LHRH) analogs and/or human chorionic gonadotropin (hCG) could theoretically increase circulating androgens that may, in turn, promote testicular descent.

Surgical options include various forms of orchiopexy or orchiectomy. Primary orchiopexy (surgical mobilization of the testicle with placement and fixation in the scrotum) is usually performed for palpable cryptorchid testicles that are of relatively normal size and appearance that are located in the inguinal canal.³ In cases in which the testicle is found to be atrophic with little or no viable germ cell tissue remaining,

orchiectomy may be performed. For nonpalpable testicles located just inside the internal inguinal ring or in the abdomen, surgical management is more complicated and is dependent on location in the abdomen and the length of the gonadal vessels. If the testicle is of normal size and appearance and if the vessels are of adequate length, primary orchiopexy is usually performed.^{3,4} If the vessels are so short as to prohibit tension-free placement of the testicle in the scrotum, 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.³

This procedure can be performed 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 as a 2-stage procedure. In a 2-stage procedure, the vessels are ligated in the first operation, the testicle is allowed to develop presumably better collateral circulation in its abdominal position and is then moved to the proper position in the scrotum during a second procedure, usually 3 to 6 months later. Both primary orchiopexy and the FS procedure can be performed using laparoscopic or open surgical technique.

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

As part of a larger systematic review of evaluation methods and treatments for cryptorchidism funded by the Agency for Healthcare Research and Quality,⁵ we assessed the effectiveness of hormone therapy and surgical approaches

for treating cryptorchidism on outcomes including testicular descent, function of testicles, further surgical intervention, infertility/subfertility, and development of testicular malignancy. We present these findings here; the full report and review protocol are available from the Agency for Healthcare Research and Quality Effective Health Care Web site (<http://effectivehealthcare.ahrq.gov>).

METHODS

Search Strategy

We searched Medline via the PubMed interface, the Cumulative Index to Nursing and Allied Health Literature, and Embase from 1980 to February 2012 by using controlled vocabulary terms and key terms related to cryptorchidism. We also hand-searched the reference lists of all included studies and of recent reviews related to cryptorchidism treatment to identify additional references.

Study Selection

Study inclusion and exclusion criteria were developed in conjunction with an expert panel of clinicians and researchers involved in treating cryptorchidism. Studies were limited to those whose participants were prepubescent boys with cryptorchidism. Studies that evaluated hormonal or surgical treatments had to include at least 1 comparison group and provide data on the position of the testicles after treatment. Two investigators independently reviewed each study against the inclusion criteria (Table 1) with disagreements resolved through adjudication by a senior investigator.

Data Extraction

Investigators extracted data using a standardized form. Data were verified by a second investigator. We collected data on study design, study population

TABLE 1 Study Inclusion Criteria: Population, Intervention, Comparator, Outcomes, Timing, Setting

Category	Criteria
Study population	Prepubescent males presenting with cryptorchidism or suspected cryptorchidism
Interventions	Hormones, including hCG or gonadotropin-releasing hormone, surgical therapy, and specific surgical techniques (ie, 1-stage versus 2-stage orchiopexy, laparoscopic versus open approach)
Comparators	Nontreatment, later treatment, hormones, and different surgical techniques
Outcomes	<ul style="list-style-type: none"> ● Immediate (within 6 wk of therapy) and short-term (6 wk to 2 y of therapy) outcomes: <ul style="list-style-type: none"> ○ Testicular size and appearance ○ Testicular position ○ Pain ○ Parent/patient satisfaction ○ Need for further surgical intervention ○ Emotional/psychosocial response ○ Adverse effects, including but not limited to pain, infection, hematoma, and edema ● Long-term (>2 y after therapy) outcomes: <ul style="list-style-type: none"> ○ Testicular size and appearance ○ Testicular position ○ Endocrine function ○ Body image ○ Parent/patient satisfaction ○ Infertility/subfertility ○ Torsion ○ Testicular malignancy and cancer ○ Hernia ○ Emotional/psychosocial response
Timing	Time frame for reporting of outcomes was not restricted.
Setting	All settings were considered, including hospitals and university or academic medical centers.

hCG, human chorionic gonadotropin.

characteristics, baseline and follow-up data on testicular position and other outcomes as available, and harms.

Study Quality Assessment

Two investigators independently assessed each study using the Cochrane Risk of Bias tool⁶ for randomized controlled trials (RCTs) and the Newcastle-Ottawa Quality Assessment Scale⁷ for cohort studies. Results were adjudicated when necessary. The domains used to assess quality for RCTs included sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting bias. For the cohort studies, the criteria included selection of study groups, comparability of study groups, and ascertainment of exposure or outcome of interest. The scores for each study were converted into a rating of “good,” “fair,” or “poor” quality.

Conversion details are provided in the full report.

The strength of evidence (SOE) reflects an assessment of the overall body of literature, and specifically reflects our confidence that the observed effect is close to the actual effect and unlikely to change with further research. We assessed SOE for the primary outcomes of treatment based on 4 major domains, including risk of bias (low, medium, or high), consistency of findings (inconsistency not present or present or unknown), directness (whether the outcome measured was the direct health outcome of interest), and precision (precise or imprecise).⁸ The overall SOE was graded “high,” indicating high confidence that evidence reflects true effect; “moderate,” indicating moderate confidence that 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.

Data Synthesis

Data on the hormonal treatments were analyzed qualitatively with the development of evidence tables. For the surgical interventions, data on proportions achieving testicular descent were pooled and the weighted proportions (sum of all successful 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.

RESULTS

Figure 1 outlines the flow of studies identified for the review. We identified 3448 unique abstracts. Of these, 14 studies met our inclusion/exclusion criteria and addressed the effectiveness of hormonal treatments, and 26 addressed outcomes of surgical interventions. Information on modifiers of hormonal and surgical treatments was available in 23 studies, and 11 studies included data on harms.

Effectiveness of Hormones for Achieving Testicular Descent

Fourteen studies in 19 publications assessed the effectiveness of hormonal therapy as a treatment of cryptorchidism. Individual studies often included multiple arms. Six studies compared LHRH with placebo, 1 compared hCG with placebo, 4 compared LHRH with hCG, and 6 compared various doses or regimens of the same agent. Of the 14 studies,

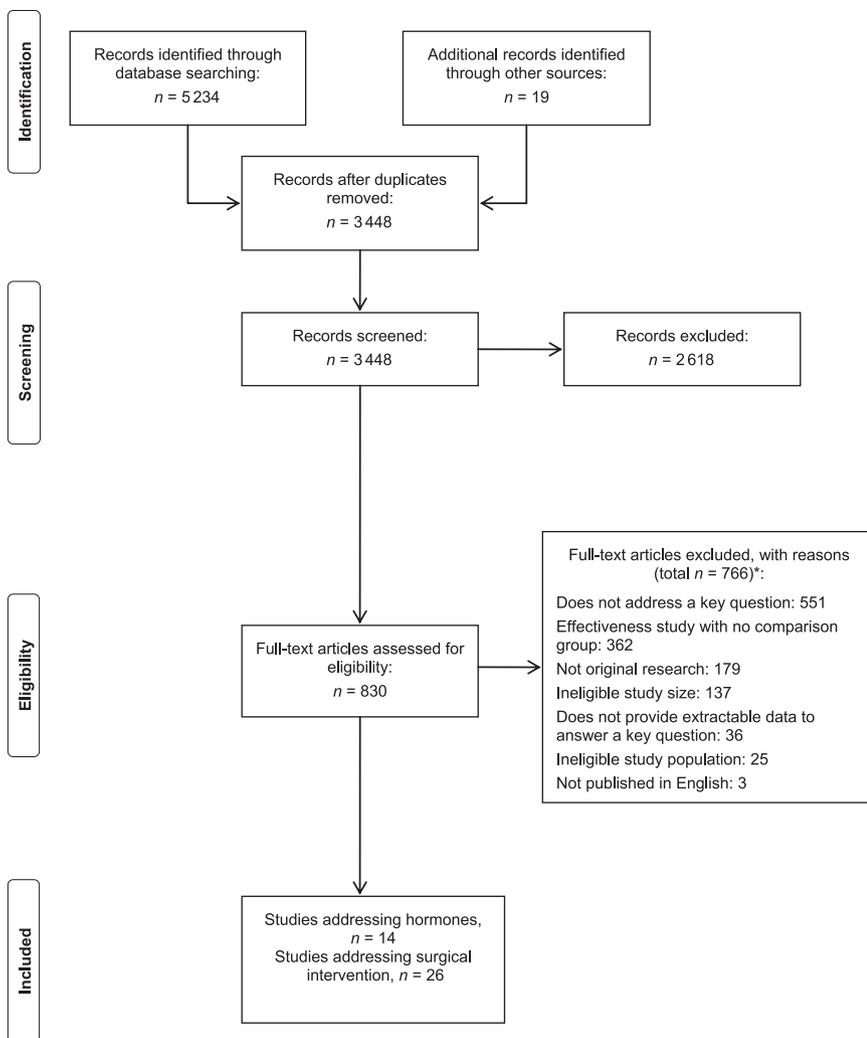


FIGURE 1 Disposition of studies identified. *Articles may be excluded for multiple reasons.

11 were RCTs,^{9–22} 2 were prospective cohort studies,^{23,24} and 1 was a retrospective cohort study.^{25,26} Three studies were of good quality,^{17,23,25,26} 2 were of fair quality,^{14,15} and 9 were of poor quality.^{9–13,16,18–22,24}

Six studies^{9–16} specifically compared successful testicular descent rates after administration of LHRH versus placebo (2 fair quality^{14,15} and 4 poor quality^{9–13,16}). Five of 6 studies concluded that LHRH was more effective than placebo in inducing testicular descent with variable reported effect sizes across studies, whereas 1 study was equivocal (see Table 2).^{12–16} In the 5 studies that appeared to show

a benefit to LHRH therapy, 4 did not assess statistical significance at all, whereas 1 failed to document statistical significance likely because of inadequate sample size. No harms of hormonal treatment were reported.

One of the studies comparing LHRH to placebo also included a third hCG arm.¹⁴ As noted previously, results comparing LHRH to placebo were equivocal, with LHRH being more effective in achieving testicular descent than placebo in patients with bilateral cryptorchidism, but no better than placebo in patients with unilateral cryptorchidism. In this study, hCG was better than placebo at achieving testicular descent in both

bilateral and unilateral patients, but the SOE was considered low (Table 3).

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.

We assessed the SOE for our primary outcome of testicular descent. There is moderate SOE for increased testicular descent with LHRH compared with placebo, low SOE for increased testicular descent with hCG compared with placebo, and low SOE for equivalence between LHRH and hCG.

No studies provided cancer or fertility outcomes for the comparisons listed, so the SOE is insufficient for these outcomes.

Effectiveness of Surgical Procedures

We identified 26 studies, including 5 RCTs and 1 prospective and 20 retrospective cohort studies, that evaluated surgical treatments.^{27–53} Four studies were judged good quality,^{27,45,49,52} 1 fair quality,³² and the remainder poor quality.^{28–31,33–40,42–44,46–48,50,51,53}

Eleven studies reported outcomes after either 1-stage FS orchiopexy, 2-stage FS orchiopexy, or primary orchiopexy.^{36–40,42–45,47,48} Nine of these studies, all retrospective cohorts, provided success rates by surgical procedure, although the choice of surgical method is made clinically and not with the intent of comparative effectiveness. Only 1 study controlled for starting testicle location.²⁸

Surgical treatment of cryptorchidism was associated with success rates of testicular descent that ranged from 33% to 100% (Tables 4, 5, and 6), depending on type of surgery. Each surgical approach was assessed independently for

TABLE 2 Short-Term Testicular Descent in Randomized, Placebo-Controlled Studies of LHRH

Study <i>n</i> Length of Follow-up Quality	LHRH Dose	LHRH Frequency	LHRH Duration	LHRH Descent, %		Placebo Descent, %
				Statistical Significance		
Olsen et al 1992 ¹⁵ <i>n</i> = 123 4 wk Fair	400 µg	3 times daily	4 wk	9.7		1.6
Christiansen et al 1988 ¹⁴ <i>n</i> = 220 4 wk Fair	200 µg	3 times daily	4 wk	9 (bilateral cryptorchidism) 0 (unilateral cryptorchidism)	<i>P</i> = .12 (95% CI: 0.1%–16.6%)	0 (bilateral cryptorchidism) 0 (unilateral cryptorchidism)
De Muinck Keizer-Schrama and Hazebroek et al 1986–1987 ^{9–11} <i>n</i> = 237 8 wk Poor	200 µg	3 times daily	4 wk	9.0	NS	8.0
Hagberg and Westphal, 1982 ¹² <i>n</i> = 50 4 wk Poor	100 µg	3 times daily	28 d	62.0	NR	3.0
Karpe et al 1983 ¹³ <i>n</i> = 50 6 mo Poor	100 µg	6 times daily	28 d	20.0	NR	12.0
Wit et al 1986 ¹⁶ <i>n</i> = 49 8 wk Poor	400 µg	3 times daily	28 d	37	NR	18
					NR	

CI, confidence interval; LHRH, luteinizing-hormone-releasing hormone; NR, not reported; NS, not significant.

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. No studies compared hormonal therapy alone to surgery.

Only 1 study assessing testicular descent was rated as good quality.⁴⁵ This study had a testicular descent rate of 63% for 1-stage FS, 67.6% for 2-stage FS, and 89.1% for primary orchiopexy, slightly lower in all types of surgery than the pooled estimate.

The weighted success rate for all 3 approaches exceeds 75%. The overall success rate for 1-stage FS is 78.7% (Table 4). The overall success rate for 2-stage FS is 86% (Table 5). The overall success rate of primary orchiopexy is 96.4% (Table 6).

Atrophy rates were reported in 5 studies and pooled results were 1.83% for primary orchiopexy (range 0%–4%, 5 studies),^{37,39,40,43,48} 28.1% for 1-stage FS (range 22%–67%, 3 studies),^{40,43,48} and 8.2% for 2-stage FS (range 0%–12%, 5 studies).^{37,39,40,43,48}

We assessed the SOE as our confidence in the weighted average of successful testicular descent associated with each surgical approach separately (Table 7). Although retrospective studies typically had high risk of bias because of

TABLE 3 Strength of Evidence of Hormonal Treatments for Cryptorchidism

No. of Studies; Total Subjects; Testes Treated	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence and Magnitude of Effect
Testicular descent					
LHRH versus placebo 6; 752; 935	RCTs/Moderate	Consistent	Direct	Imprecise	Moderate LHRH: 9%–62% Placebo: 0%–18%
hCG versus placebo 1; 243; 280	RCT/Moderate	Unknown	Direct	Unknown	Low Bilateral: 23% vs 0% Unilateral: 15% vs 0%
LHRH versus hCG 3; 431; 465	RCT/Low	Inconsistent	Direct	Imprecise	Low RCT: LHRH: 0%–18.8% hCG: 5.9%–23.0%
LHRH versus hCG 1; 324; 198	Cohort/High	Consistent	Direct	Imprecise	Cohort: LHRH: 29.4% hCG: 34.5%

hCG human chorionic gonadotropin; LHRH Luteinizing-hormone-releasing hormone; RCT randomized controlled trial.

TABLE 4 Success Rates After 1-Stage FS

Author and Country	Quality	Total Participants	Total Testicles	% Success (<i>n</i> Testicles Treated)
Stec et al 2009 ⁴⁵ United States	Good	136	156	63 (27)
Baker et al 2001 ⁴⁸ United States	Poor	226	263	74.1 (27)
Chang et al 2001 ⁴⁴ United States	Poor	80	92	84 (19)
Chang et al 2008 ⁴⁷ United States	Poor	48	48	94.3 (35)
Compløj et al 2011 ³⁶ Austria	Poor	41	50	79 (33)
Denes et al 2008 ⁴³ Brazil	Poor	46	54	33 (3)
Kim et al 2010 ³⁸ South Korea ^a	Poor	67	86	82 (11)
Pooled %		Total: 644	Total: 749	78.7

All studies were retrospective cohorts.

^a Controlled for location.

lack of a control group, in grading the overall SOE, 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, SOE might be considered high because of the high magnitude of effect when compared with an implicit control.

For the outcome of testicular descent, SOE was moderate for 1- and 2-stage orchiopexy and high for primary orchiopexy. All studies were retrospective cohort studies, and thus had high risk of bias, but we deemed these to be an appropriate study design for the question of ability of orchiopexy to achieve testicular descent and considered the relative challenges of this design to be outweighed by the magnitude of effect. Primary orchiopexy had higher SOE than 1-stage and 2-stage procedures based on the higher number of testicles (outcomes) reported in the literature.

We also assessed SOE for the outcome of testicular atrophy, and on the same methodological basis as was used for testicular descent, found the SOE to be low for a 28.10% atrophy rate with 1-stage FS, low for an 8.20% atrophy rate with 2-stage FS, and moderate for a 1.83% atrophy rate for primary orchiopexy.

Effectiveness of Surgical Approach (Open Versus Laparoscopic)

Five studies compared an open versus laparoscopic approach for the same procedure (1 good,²⁷ 1 fair,³² and 3 poor quality^{28,50,51}). Two studies noted success rates for laparoscopic surgeries similar to those of open surgeries.^{27,50} One fair-quality cohort study reported that participants undergoing a laparoscopic approach “had less pain when compared to the open technique in 80% of cases” using a visual analog scale, but how this comparison was made is unclear. Similarly, although the

authors note that all patients had “satisfactory results in relation to size and location of testicle,” details regarding these outcomes are lacking.³² Another poor-quality cohort study that included both palpable and nonpalpable testicles, failed to control for the location of the testicle in the analysis, and grouped both primary and FS orchiopexies into two heterogeneous groups based on whether an open or laparoscopic approach was used, making it difficult to draw meaningful conclusions in terms of postoperative testicular position or viability.⁵¹

Finally, 1 poor-quality RCT compared outcomes after various types of laparoscopic or open orchiopexies for nonpalpable testicles.²⁸ This study is one of the few reports in the literature that controlled for location of the testicle within the abdomen, allowing for comparisons between procedures and minimizing the possibility of confounding by indication. If a testicle was noted via laparoscopic evaluation to be high in the abdomen, the patient underwent a laparoscopic 1-stage FS procedure (laparoscopic clipping of the testicular vessels). Patients were then randomized to receive either open or laparoscopic 2-stage FS orchiopexy.

Perioperative outcomes between participants undergoing laparoscopic or open second procedures were compared, with patients undergoing laparoscopic 2-stage FS orchiopexy noted to have statistically significantly shorter operative times ($P = .000$), time to oral feeding ($P = .004$), hospital stays ($P = .008$), and return to normal activities ($P = .000$). Although all testicles in both groups were noted to have satisfactory scrotal position after surgery, 2 (10%) of the 20 testicles in the laparoscopic arm and 3 (19%) of the 16 testicles in the open arm had atrophied after 1 year of follow-up. Patients in this study who had viable testicles located

TABLE 5 Success Rates After 2-Stage FS

Author and Country	Quality	Total Participants	Total Testicles	% Success (<i>n</i> Testicles)
Stec et al 2009 ⁴⁵ United States	Good	136	156	67.6 (37)
Baker et al 2001 ⁴⁸ United States	Poor	226	263	87.9 (58)
Chang et al 2001 ⁴⁴ United States	Poor	80	92	86 (7)
Chang et al 2008 ⁴⁷ United States	Poor	48	48	80 (10)
Compløj et al 2011 ³⁶ Austria	Poor	41	50	82 (17)
Denes et al 2008 ⁴³ Brazil	Poor	46	54	88 (25)
Dhanani et al 2004 ⁴² United States	Poor	74	83	98 (49)
Kim et al 2010 ³⁸ South Korea ^a	Poor	67	86	67 (3)
Moursy et al 2011 ³⁷ Egypt	Poor	66	76	88.8 (36)
Pooled %		Total: 784	Total: 908	86.0

All studies were retrospective cohorts.

^a Controlled for location.

TABLE 6 Success Rates After Primary Orchiopexy

Author and Country	Quality	Total Participants	Total Testicles	% Success (n Testicles Treated)
Stec et al 2009 ⁴⁵ United States	Good	136	156	89.1 (92)
Baker et al 2001 ⁴⁶ United States	Poor	226	263	97.2 (178)
Chang et al 2001 ⁴⁴ United States	Poor	80	92	100 (66)
Denes et al 2008 ⁴³ Brazil	Poor	46	54	96 (26)
Dhanani et al 2004 ⁴² United States	Poor	74	83	100 (28)
Kim et al 2010 ³⁸ South Korea ^a	Poor	67	86	98 (49)
Moursy et al 2011 ³⁷ Egypt	Poor	66	76	100 (28)
Pooled %		Total: 695	Total: 810	96.4

All studies were retrospective cohorts.

^a Controlled for location.

in the lower portion of the abdomen (close to the inguinal ring) were randomized to undergo either laparoscopic or open primary orchiopexy. Like the high abdominal group, patients randomized to laparoscopic orchiopexy had statistically superior perioperative outcomes. Of the 21 testicles randomized to laparoscopic orchiopexy and the 18 randomized to open orchiopexy, all were satisfactorily placed in the scrotum and no cases of atrophic testicles were noted after 1 year of follow-up.

We assessed the SOE for equivalence of laparoscopic and open approaches for achieving testicular descent to be low with only 1 RCT²⁸ of poor quality and 2

cohort studies of fair³² and poor⁵¹ quality, although the individual studies report that success rates are similar with both approaches. Similarly, SOE was low for the effect of the approach on atrophy (Table 7).

There are few studies comparing the effectiveness of interventions on future fertility associated with treatment of cryptorchidism. Furthermore, in those studies (where the participants are adults who had cryptorchidism in childhood), the primary outcome is usually semen analysis parameters, which is at best a proxy for fertility. One study examined ability to father children and focused on the addition of

hormonal therapy to surgery, finding 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. To this end, no data are available to assess whether 1 approach is superior for fertility outcomes, although it is accepted that untreated cryptorchidism is associated negatively with later fertility.

Harms of Treatments

Eleven studies of hormonal and surgical interventions included harms; 2 studies were of good quality,^{17,52} 2 were of fair quality,^{14,15} and 7 were of poor quality.^{12,13,16,18,24,37,48} Eight^{12–18,24} of 14 hormonal studies reported harms. The most common outcomes were virilizing effects (eg, hair, increase in penis size, and erections), and behavioral changes (eg, aggression). Of the 8 hormonal studies reporting harms, 2 did not segregate data by study arm, and thus harms could have presented in either a treatment or placebo arm.^{17,24} One study reported that 74% of 116 boys receiving hCG had virilizing effects, compared with 5.1% of boys

TABLE 7 Strength of Evidence of Surgical Treatments for Cryptorchidism

No. of Studies; Total Subjects; Treated Testicles	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence and Magnitude of Effect ^a
Testicular descent					
1-stage FS 7; 644; 155	Retrospective cohorts/ High	Consistent	Direct	Imprecise	Moderate 78.7% (range: 33%–94.3%)
2-stage FS 9; 784; 242	Retrospective cohorts/ High	Consistent	Direct	Imprecise	Moderate 86.0% (range: 67%–98%)
Primary orchiopexy 7; 695; 467	Retrospective cohorts/ High	Consistent	Direct	Precise	High 96.4% (range: 89.1%–100%)
Open versus laparoscopic repair 1; 75; 75	RCT High	Unknown	Direct	Unknown	Low RCT: No difference in postoperative testicular position
Open versus laparoscopic repair 2; 96; 110	Cohorts/High	Consistent	Direct	Imprecise	Cohorts: No difference in postoperative testicular position
Atrophy					
1-stage FS 3; 320; 32	Retrospective cohorts/ High	Consistent	Direct	Imprecise	Low 28.1% (range: 22%–67%)
2-stage FS 5; 470; 158	Retrospective cohorts/ High	Consistent	Direct	Precise	Low 8.2% (range: 0%–12%)
Primary orchiopexy 5; 470; 273	Retrospective cohorts/ High	Consistent	Direct	Precise	Moderate 1.83% (range: 0%–4%)
Open versus laparoscopic repair ^b 1; 75; 75	RCT High	Unknown	Direct	Unknown	Low Laparoscopy: 10% Open: 19%

^a Pooled proportion (range).

^b Atrophy rates for second-stage orchiopexy; no atrophy reported with primary orchiopexy.

receiving only LHRH, but 1 of the hCG arms also included LHRH and another included human menopausal gonadotropin.¹⁸ All side effects had receded by the 6-month follow-up. No other study reported side effects to be as common as virilization. Reported harms of hormonal treatments were mild and transient and had receded by 6 months.

Three studies reported harms associated with laparoscopic surgery.^{37,48,52} Rare cases of intestinal injury due to Veress needle puncture (1 case),⁴⁸ postoperative laparoscopic port site reducible (3 cases),⁵² and incarcerated (2 cases) hernia³⁷ were noted with laparoscopy. 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

The goal of any intervention for cryptorchidism is to move the undescended testicle to a normal position in the scrotum, in as safe and least invasive way possible. Although there are a number of therapeutic options available to parents and providers, our study found that the current literature on comparative effectiveness may not provide definitive answers for those seeking to provide guidance in clinical decision-making. Specifically, only 7 studies identified in our analysis were of good quality^{17,23,25–27,45,49,52} and this is reflected in the SOE, which was generally low to moderate for any intervention and outcome. This, in turn, underscores the need for further research.

In the case of hormonal treatment, most studies were of poor quality, precluding definitive conclusions as to a specific expected effect rate for any hormone or combination thereof. Acknowledging this, studies report

slightly higher rates of testicular descent for LHRH and hCG compared with placebo and seem to suggest that lower initial location of the testicle may be associated with a greater likelihood of success (although none of the studies was sufficiently powered for this assessment). In addition, some harms of treatment were also noted. Specifically, some studies reported more frequent temporary virilizing side effects, including increased penile length, erections, and testicular enlargement, although all side effects were transitory.

With regard to the surgical treatment of cryptorchidism, all approaches were associated with success rates of 75% or higher. When surgically treating boys with cryptorchidism, providers must select both a specific procedure (primary orchiopexy, 1- or 2-stage FS orchiopexy, or orchiectomy) and approach (open versus laparoscopic). In the case of specific procedures, although the fairly substantive observational literature reviewed here reports outcomes after various types of orchiopexies, the fact that the choice of procedure is based primarily on the initial location of the testicle makes comparing the results of studies difficult. Specifically, primary orchiopexy is more likely to be used in cryptorchid testes found to be in lower positions, closer to the scrotum, increasing the likelihood of success. Conversely, FS orchiopexies (whether 1 or 2 stage) tend to be reserved for higher-located testicles, which, by their nature, are more difficult to treat and more likely to retract back to an abnormal position after surgery. To this end, the observation that primary orchiopexy is associated with higher success rates when compared with the FS approach is more likely due to underlying baseline differences in patients undergoing this procedure than true differences in the effectiveness of the technique. That

being said, SOE was high only for the effect of primary orchiopexy on testicular descent, for which the most data are available.

There is increased use of laparoscopic techniques throughout pediatric surgery, primarily because of technological advances coupled with the commonly accepted belief that it is less invasive and, therefore, better tolerated by patients. The literature comparing open to laparoscopic surgery in cryptorchidism appears to indicate that success rates are at least comparable between the 2 approaches, although it is worth noting that the SOE was low. There appeared to be some evidence that patients undergoing laparoscopy reported shorter convalescence and less postoperative pain; however, certain studies reported rare harms that were unique to laparoscopic surgery, such as hernia at the port site or Veress needle injury.

Despite the low SOE associated with the literature on laparoscopy in cryptorchidism, it is clear that this approach plays an important role in the diagnosis and treatment of cryptorchidism. In 2013, diagnostic laparoscopy is almost always the approach of choice when attempting to localize a nonpalpable cryptorchid testicle thought to be potentially located in the abdomen. As evidence, all but 1 of the studies in our review published in the past 5 years that included assessment of the abdomen for a nonpalpable testicle^{28,32,36–38,43,47,51} used laparoscopy for this part of the procedure, even if they used an open technique to repair the cryptorchidism.

Clearly, the existing evidence leaves many questions regarding the optimal approach to the treatment of cryptorchidism unanswered. In the case of hormonal therapy, most studies have focused primarily on LHRH and its agonists because it is easily administered intranasally. A wide range of

success rates is seen across studies, possibly owing to heterogeneity in the study populations or potentially owing to variability in drug absorption through the intranasal route. Some literature suggests that differences may be because of 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. Given that 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 what the possibility of success is with this treatment, as even a small likelihood of success coupled with the avoidance of surgery may be appealing.

Because most reviewed studies of surgery were observational, the potential for confounding and effect measure modification in this literature to obscure true effects is significant. Studies intended to address comparative effectiveness of treatment in this condition, including 1-stage versus 2-stage FS orchiopexy for nonpalpable abdominal testicles should either use a randomized design or carefully control for covariates, such as testicular location, size and appearance, ectopia,

and unilateral or bilateral disease. This is particularly important for initial testicular location, which may be both a modifier of effectiveness and a factor used to choose the surgical procedure. Finally, these studies must include follow-up for at least 6 to 12 months to observe for delayed atrophy of the testicle.

The literature available to assess treatment of cryptorchidism also is characterized by a lack of standardization of outcomes. Studies routinely use the term “success rates” but fail to define a successful outcome. In some cases, the authors report success rates as proper placement of the testicle in the scrotum in the early postoperative period and then report ≥ 6 -month atrophy rates separately. Given that the goal of the procedure is usually to place the testicle in the scrotum and to maximize long-term endocrine function and fertility, the definition of success should always reflect both of these important end points (testicular location and size), and we encourage researchers to report both.

CONCLUSIONS

Hormonal treatment is marginally effective relative to placebo, with moderate SOE, but is successful in some

children and with minimal side effects, suggesting that it may be an appropriate trial of care for some patients. If successful, these patients should continue to be monitored for late re-ascent, as most of the studies on this issue did not include long-term follow-up. Surgical options appear effective, with rates of normal postoperative scrotal position $>75\%$. Our ability to draw definitive conclusions regarding the comparative effectiveness of the surgical approaches is limited by confounding by indication in the individual studies, which also affects the quality of the literature. The strength of the evidence for the effects of either 1-stage or 2-stage FS procedures on testicular descent is moderate (low for atrophy) and high for primary orchiopexy (moderate for atrophy). Comparable outcomes have been seen with laparoscopic and open approaches to surgical repair (low SOE for testicular descent and atrophy in studies comparing these approaches).

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