Preoperative Hormonal Stimulation In Hypospadias: A Systematic Review

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Summary

Introduction: Preoperative hormonal stimulation with testosterone or estrogen is an emerging treatment modality for hypospadias, which can potentially improve surgical outcomes and reduce the risk of complications. This review aims to evaluate the current knowledge on preoperative hormonal stimulation in hypospadias. **Methods:** This study was a combination of a systematic review followed by a meta-regression analysis performed on PubMed, Google Scholar, DOAJ, and Cochrane. The study included randomized controlled trials, prospective and retrospective cohort studies, and before-and-after studies with or without control. The search was performed in English and was limited to articles published between January 1, 2000, and December 31, 2020. **Results:** The database search yielded 188 articles, which were systematically eliminated, leaving 15 relevant articles. The analyzed articles showed that testosterone is the most commonly used hormonal treatment in hypospadias, followed by dihydrotestosterone (DHT) and estrogen. Testosterone may be given in topical, parenteral, or oral formulations, while DHT is most often used in topical form. **Conclusions:** Preoperative stimulation with testosterone or DHT is associated with increased penile length and glans circumference before surgery, which may ease the reconstruction process. In addition, testosterone and DHT increase the rate of neovascularization and reduce the risk of postoperative complications.

Keywords: Hypospadias, Preoperative hormonal stimulation, Androgen, Testosterone, Dihydrotestosterone, Repair

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Introduction

Hypospadias is one of the most common congenital urological abnormalities in men. Hypospadias is characterized by proximal displacement of the external urethral meatus, penile curvature, and ventral foreskin deficiency (1). In about 70% of cases, the external urethral meatus is located on the distal side of the body of the penis and is generally not accompanied by other urogenital deformities (1, 2). However, in a minority of cases, hypospadias can be found on the proximal penis and may be accompanied by other urogenital deformities, including disorders of sexual differentiation and undescended testis (1, 3). The etiology of

hypospadias is still not fully identified, but a genetic predisposition, as well as hormonal, is known to influence the incidence of hypospadias (4).

The main goal of hypospadias repair is to achieve a normal urethral function and an excellent cosmetic appearance. Indications for hypospadias repair include a proximally located meatus, a ventrally deflected urinary stream, meatal stenosis, curved penis, cleft glans, a rotated penis with an abnormal cutaneous raphe, a preputial hood, penoscrotal transposition, and split scrotum (5). Currently, available guidelines recommend hypospadias repair at 6–18 months of age, depending on the severity of the hypospadias and the need for repeat procedures. Anesthesia risks, tissue availability, and the psychological effects of genital surgery should also be considered in hypospadias repair (1).

Several studies have used hormonal stimulation to improve cosmetic and functional outcomes after hypospadias repair. Androgen stimulation can increase the phallic growth rate, facilitating reconstruction and reducing complications. Administration of testosterone, dihydrotestosterone (DHT), and human chorionic gonadotropin (hCG) may increase penile length, glans circumference, and tissue vascularity before surgery. However, the objective benefits of preoperative hormonal therapy in hypospadias cases are unclear. This study aims to analyze the current information available in the literature regarding the use of hormonal stimulation as preoperative therapy in hypospadias.

Materials and Methods

This study combined a systematic review followed by a meta-regression analysis. It was performed on the PubMed, Cochrane Database of Systematic Reviews, Google Scholar, and Directory of Open Access Journals (DOAJ) database. The search was conducted in English, using keywords related to hormonal stimulation in hypospadias patients, including *hypospadias, preoperative, stimulation, hormonal, androgens, testosterone, dihydrotestosterone,* and *estrogen*. The search was performed with a combination of some or all of these keywords, both in the title and abstract of the article. The search was limited to publications from January 1, 2000, to December 31, 2020.

The study designs included in this study were before-and-after studies with or without controls, retrospective, and prospective cohort studies, interrupted time series analysis, and randomized controlled trials. Studies on interventions in adult and pediatric patients were included if there were complete data on pediatric patients. Literature review articles, case series, letters, notes, conference abstracts, and conference articles were excluded. Data were extracted using a standardized table that includes the name of the authors, year of publication, study design, study setting, number of subjects, the treatment used, and the key findings of each study. After searching and filtering articles based on the search keywords, article analysis was done manually by considering the titles and abstract's relevance. Articles that meet the inclusion and exclusion criteria but are unclear were analyzed further by reading the full text and entering the relevant information in the data extraction table. The results obtained in the included studies were compared with those of other systematic reviews and literature. Meta-regression analysis was performed to explore the potential determinants of heterogeneity, in supposedly three variables.

The post-operative period was uneventful, abdominal drain was removed on post-operative day 2, and the patient was discharged home on post-operative day 5. Subsequently, the biliary stent was removed 12 weeks later. The patient has since been on follow-up at the surgical outpatient clinic and is symptom-free.

Results

A systematic search was carried out and yielded 188 articles (Fig. 2). A total of 171 articles remained, after rechecking and excluding duplicated articles. A total of 33 articles were eligible for this study. Then, after a comprehensive review of the full-text articles, the remaining 15 articles were included in this study. The database search results are given in Table 1 and Figure 2. The summary of each included study is shown in Table 2.

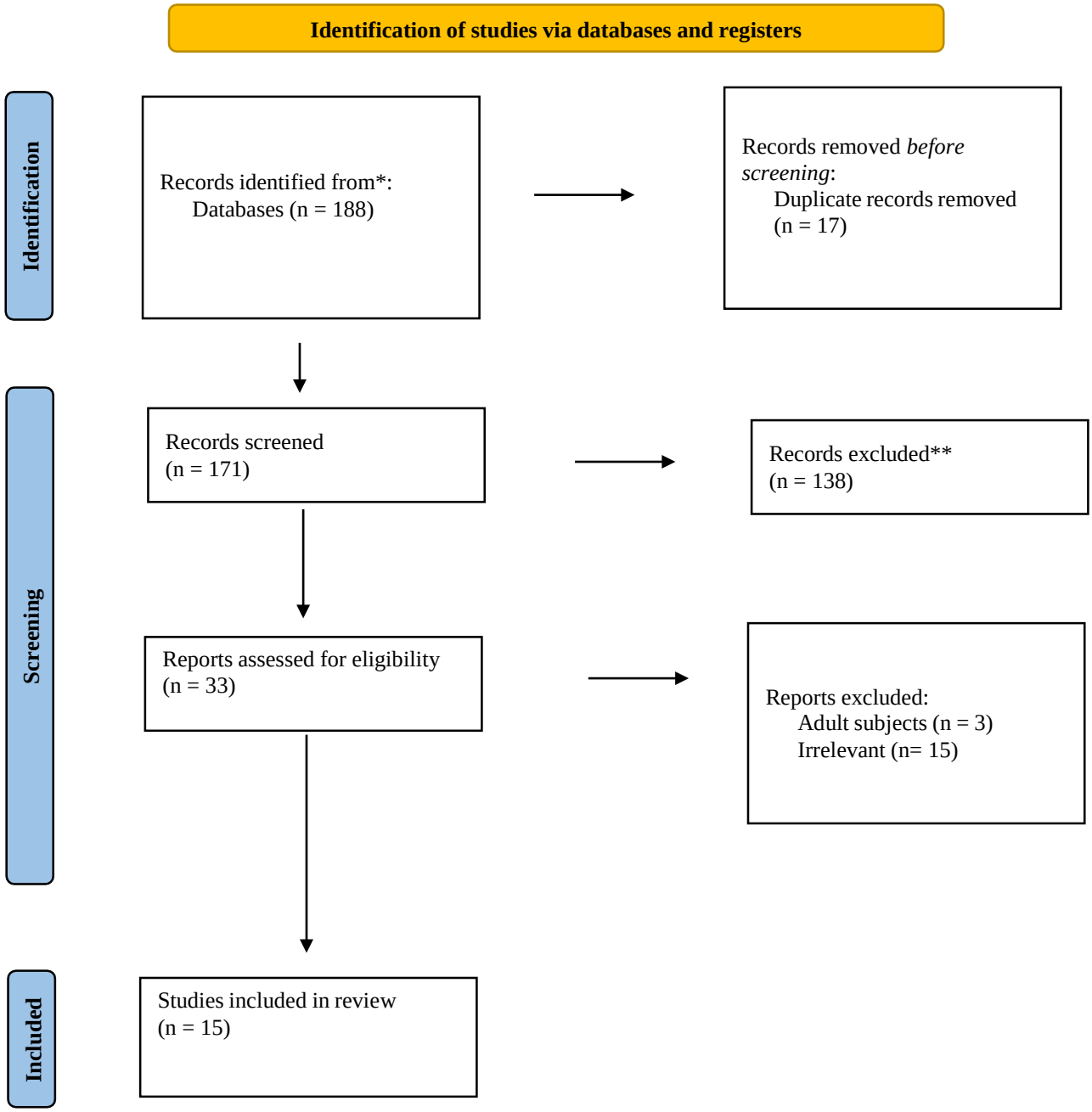

Figure 1 Study flow chart

Table 1. S udy c haract ristics and finc ings

AUTHOR	YEAR	DESIGN	SETTING	SUBJECTS	PATIENT AGE	TYPES OF HYPOSPADIAS	TREATMENT	KEY FINDINGS	SIGNIFICANCE
Gorduza et al.	2011	Pros. cohort	Single center	300	Not stated	300 cases of "severe hypospadias"	Intramuscular hCG 1.500 IU every 2 days for 6 days + intramuscular testosterone 100 mg/m2/month for 2–6 months	Lower post-operative complications in androgen stimulated group	Not significant
Gorduza et al.	2020	RCT	Multi-center	241	17.5 ± 5.1 months	241 cases of "severe hypospadias"	Topical promestriene 1%, twice daily for 2 months	Promestriene did not cause a significant change in complication risks compared with control	Not significant
Kaya et al.	2008	RCT	Single center	75	30.8 ± 5.4 months (Treatment group) 35.1 ± 5.1 months (Control group)	58 coronal, 15 penile, 2 penoscrotal	DHT gel 2.5% once daily for 3 months	The risk of wound dehiscence and scarring is lower in treatment group compared with control. DHT reduced the need for repeat surgery and provided better cosmetic results	Risk of complications not significant, need of reoperation significant
De Andrade et al.	2016	RCT	Multi-center	35	6 months–9 years	Not stated	Testosterone propionate ointment 1%, twice daily for 30 days	Significant increase in serum testosterone after 30 days in the treatment group. Mild systolic blood pressure increase in treatment group after 30 days	Significant
Rynja et al.	2017	Ret. cohort	Single center	121	0.9–1.6 years (Treatment group) 0.9–3.9 years (Control group)	19 proximal. 12 patients midshaft, 90 distal	Combination testosterone cream, 5%, twice daily or intramuscular combination testosterone, 25 mg/week for 2–3 weeks	No significant differences in complication rates between the two groups. No significant long-term side effects identified	Not significant
Babu et al.	2017	RCT	Single center	200	9 months at start of treatment	200 cases of distal hypospadias	Testosterone enanthate, 2 mg/kg/month for 3 months	83% of patients showed a significant increase in penile length and glans circumference. Lower complication and repeat surgery rates in treatment group	Significant
Luo et al.	2001	Ret. cohort	Single center	25	6–18 months	8 penile, 14 penoscrotal, 2 perineal	Testosterone enanthate, 25 mg/month for 3 months	Significant increase of penile length and circumference. Most patients experienced significant growth after first dose and needed no further doses. No significant side effects identified	Significant

RCT, randomized controlled trial; hCG, human chorionic gonadotropin; DHT, dihydrotestosterone.

Table 2. Study characteristics and findings

AUTHOR	YEAR	DESIGN	SETTING	SUBJECTS	PATIENT AGE	TYPES OF HYPOSPADIAS	TREATMENT	KEY FINDINGS	SIGNIFICANCE
Paiva et al.	2016	RCT	Single center	69	6 months–10 years	45 anterior, 13 midshaft, 11 proximal	Testosterone propionate ointment 1% or estradiol cream 0.01%	Significant increase of penile length and circumference in treatment group. Most common complications include pubic hair growth and genital pigmentation	Significant
Casali et al.	2019	RCT	Single center	33	4.01 ± 2.92 years	13 coronal, 14 subcoronal, 5 midshaft	Testosterone propionate ointment 1% or estradiol cream 0.01%	Highest epidermal thickness and type 1 collagen expression in estradiol group	Increase in type I collagen significant Increase in type III collagen not significant
McNamara et al.	2015	Ret. cohort	Single center	134	Median 8.8 months at surgery	Not stated	Topical or intramuscular testosterone	Preoperative testosterone reduces the risk of complications by 27%	Risk of complications not significant, need of reoperation significant
Menon et al.	2016	RCT	Single center	94	1–12 years	94 distal	Intramuscular testosterone enanthate 2 mg/kg/month for 3 months	Significant increase in penile length and circumference, increase of vascular proliferation, and more severe post-operative edema in treatment group	Significant
Asgari et al.	2015	RCT	Multi-center	182	18–52 months	126 midshaft, 56 distal	Intramuscular testosterone enanthate 2 mg/kg/month for 2 months	Significant increase in penile length and circumference in treatment group. Higher complication rates in control group. Main side effects include genital pigmentation and pubic hair growth	Significant
Mohammadipour et al.	2020	RCT	Single center	41	3 months–10 years	Not stated	Intramuscular testosterone 25 mg/month for 3 months	Significant glans diameter after the first dose without significant morphological changes in subsequent doses. Side effects occurred in 27.8% patients	Significant
Jonuzi et al.	2019	RCT	Single center	79	7.3 ± 6.3 months (Treatment group) 39.1 ± 5.9 months (Control group)	31 coronal, 48 penile	DHT gel 2.5% twice daily for 1 month	Significantly lower repeat surgery rates in treatment group	Significant
Chen et al.	2015	RCT	Single center	72	21.6 ± 14.3 months (Treatment group) 24.2 ± 15.7 month (Control group)s	Not stated	Oral testosterone undecanoate 2 mg/kg daily for 3 months	Significant increase in penile length and diameter, lower rates of stricture complications in treatment group. Significant difference in reoperation rates between treatment and control groups	Significant

RCT, randomized controlled trial; DHT, dihydrotestosterone.

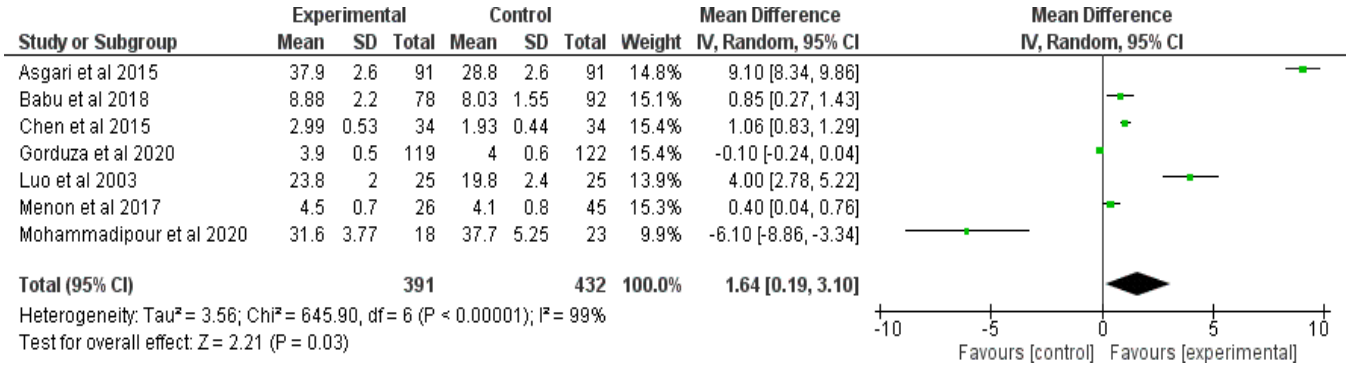

Figure 2 Forest plot for penile length

Figure 2 shows that from 15 articles seven articles include the mean and standard deviation for the penile length. The results of the meta-analysis using a random effect approach showed that the overall mean difference was 1.64 (95% CI 0.19–3.10), meaning that preoperative hormonal administration was proven to be significantly able to provide a higher average effect on penile length, by 1.64 times compared with no hormone administration. Statistical analysis showed very significant results ($p < 0.00001$) and heterogeneity (I^2) of 99% showed heterogeneous data distribution (random effect model).

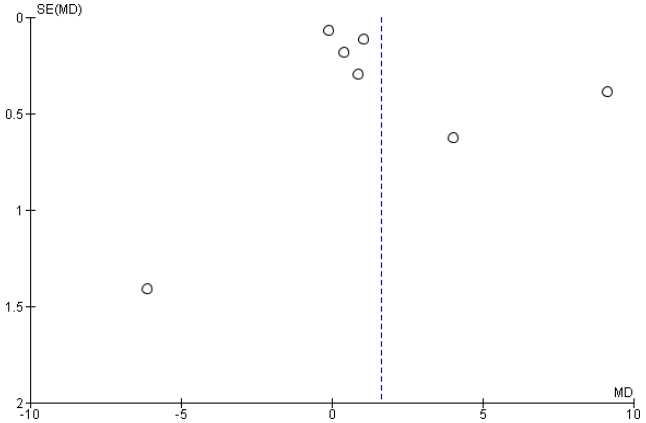

Figure 3 Funnel plot for penile length

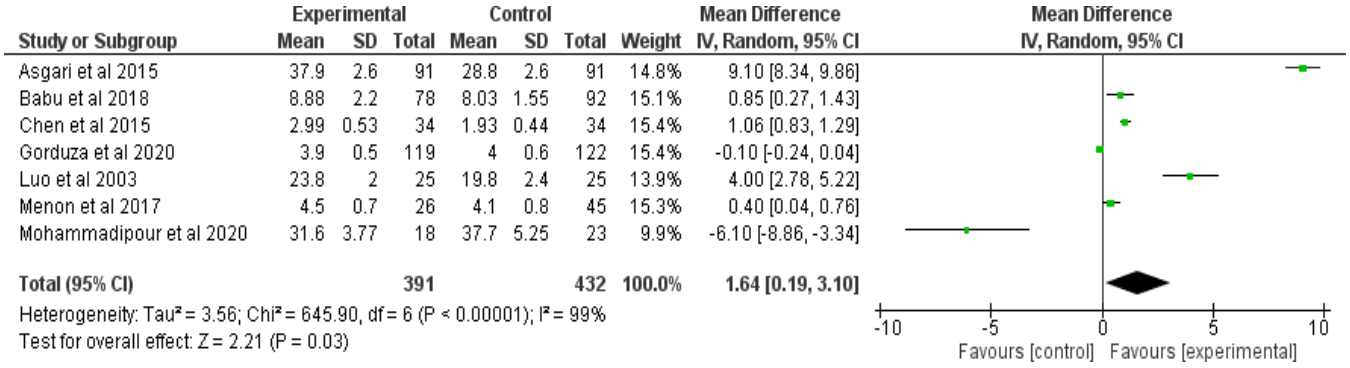

Figure 4 Gland circumference

The analysis in Figure 3 shows a possibility of publication bias with an asymmetric axis indicated by the distribution of five funnel plots on the left and two funnel plots on the right. The standard error of the left funnel plot is 0.1–1.45 and the standard error of the right funnel plot is 0.4–0.6.

Figure 4 shows that from 15 articles seven articles include the mean and standard deviation values for gland circumference. The results of the meta-analysis with the

random effects approach showed that the overall mean difference was 2.34 (95% CI 1.58–3.10), meaning that preoperative hormonal administration was proven to be significantly able to provide a higher average effect on gland circumference by 2.34 times compared with no hormone administration. Statistical analysis showed very significant results ($p < 0.00001$) and heterogeneity (I^2) of 99% showed heterogeneous data distribution (random effect model).

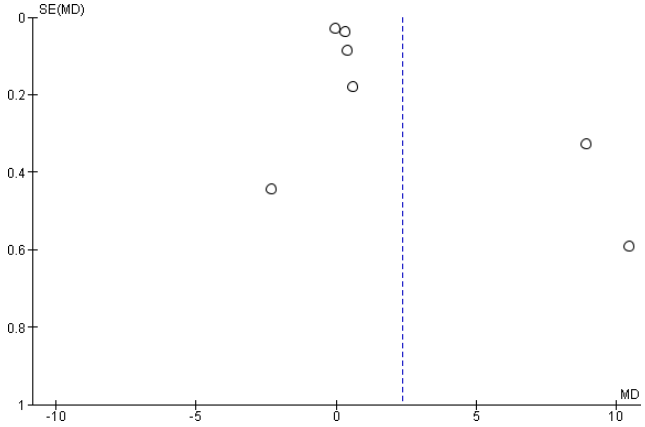

Figure 5 Funnel plot for gland circumference

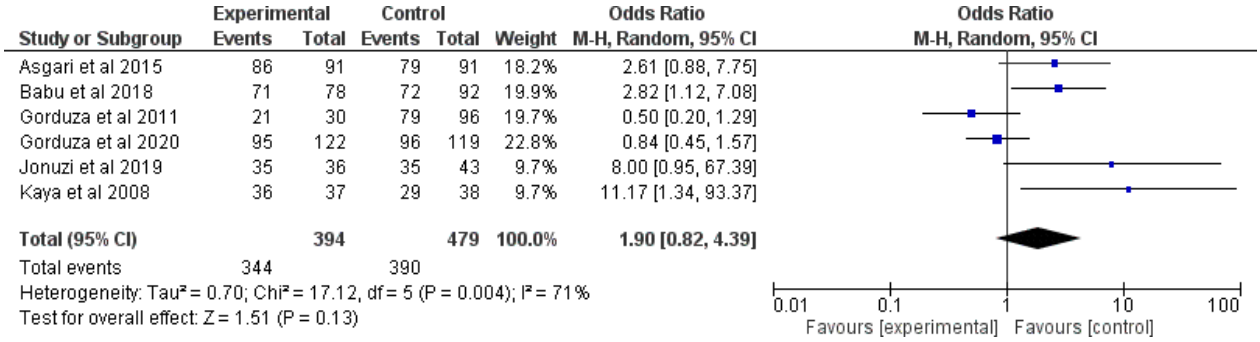

Figure 6 Forest plot for the success rate

The analysis in Figure 5 shows a possibility of publication bias with an asymmetric axis indicated by the distribution of five funnel plots on the left and two funnel plots on the right. The standard error of the left funnel plot is 0.05–0.45 and the standard error of the right funnel plot is 0.3–0.55.

Figure 6 shows that from 15 articles six articles include the percentage of success rate in preoperative hormone administration. The results of the meta-analysis with the random effects approach showed that the overall odds ratio value from the effect estimate was 1.90 (95% CI 0.82–4.39), meaning that the administration of preoperative hormonal significantly had a success rate of 1.90 times higher compared with the group that was not given preoperative hormones. Statistical analysis showed significant results ($p = 0.004$) and heterogeneity (I^2) of 71% showed heterogeneous data distribution (random effect model).

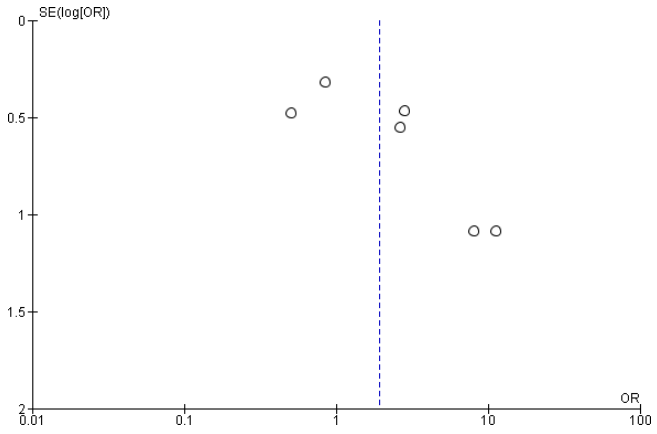

Figure 7 Funnel plot for success rate

The analysis in Figure 7 shows that there is a possibility of publication bias with an asymmetric axis shown by the distribution of two funnel plots on the left and four funnel plots on the right. The standard error of the left

funnel plot is 0.3–0.5 and the standard error of the right funnel plot is 0.45–1.1.

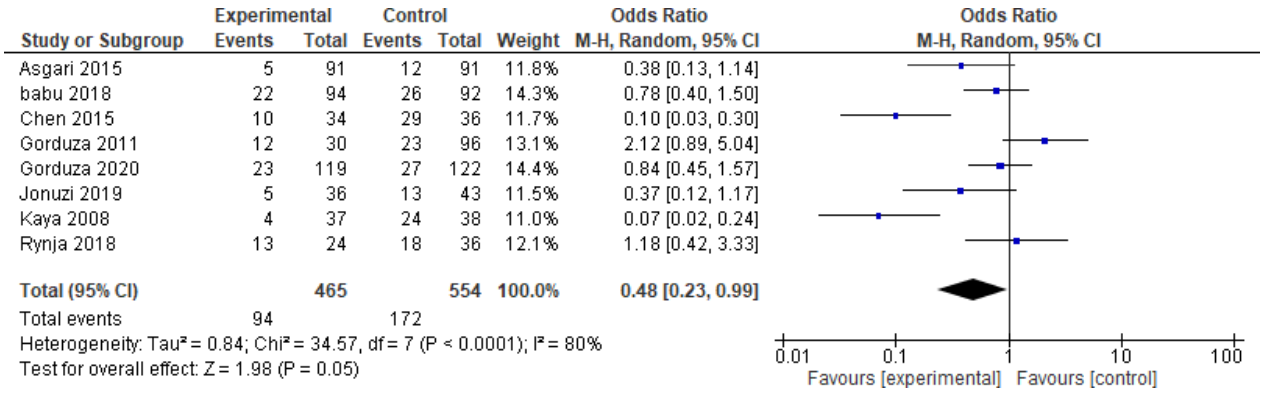

Figure 8 Forest plot for complications rate

Figure 8 shows that from 15 articles there are 8 articles that include the percentage of complications rate in preoperative hormone administration.

The results of the meta-analysis with the random effects approach showed that the overall odds ratio value from the effect estimate was 0.48 (95% CI 0.23–0.99), meaning that the administration of preoperative hormonal significantly had a complications rate of 0.48 times lower compared with the group that was not given preoperative hormones. Statistical analysis showed very significant results ($p < 0.0001$) and heterogeneity (I^2) of 80% showed heterogeneous data distribution (random effect model).

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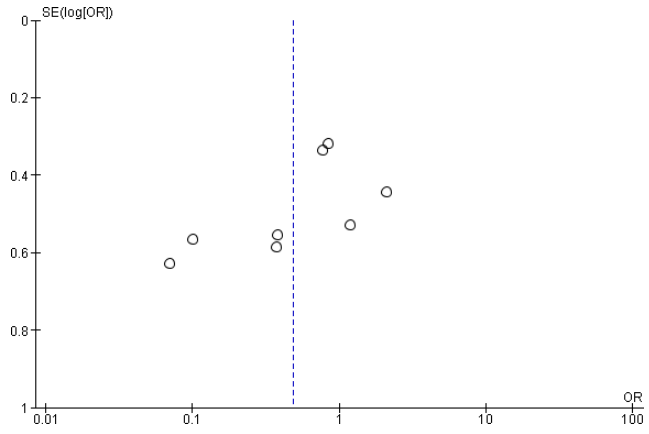

Figure 9 Funnel plot for complication rate

The analysis in Figure 9 shows that there is no publication bias with an asymmetric axis indication shown by the distribution of four funnel plots on the left and four funnel plots on the right. The standard error of the left funnel plot is 0.55–0.6 and the standard error of the right funnel plot is 0.3–0.5.

Included Articles

Of the 15 included studies, 11 were randomized controlled trials, 3 were retrospective cohort studies, and 1 was a prospective cohort study. Followed by the meta-analysis, consisting of 7 articles for penile length, seven articles for gland circumference, and six article success rate.

Populations of Included Articles

A total of 1701 patients were involved in the 15 included studies. Most of the studies involved pediatric patients under 12 months of age, and there was one retrospective study involving adult patients with a history of hypospadias repair with hormonal therapy; 12 studies were single-center studies, and 3 studies were multi-center studies.

Types of Hypospadias

Hypospadias classification varied between the included studies. Nevertheless, it appears that the majority of cases were distal hypospadias. Luo et al. reported 8 (33.3%) penile, 14 (58.3%) penoscrotal, and 2 (8.3%) perineal hypospadias patients (6). Gorduza et al. reported 300 cases of "severe hypospadias" in 2011, and another series of 241 cases in 2020, although these cases were not further classified (7, 8). Babu et al. reported a

series of 200 patients with distal hypospadias (9). The study by Casali et al. reported 13 (41%) patients with coronal hypospadias, 14 (44%) patients with subcoronal hypospadias, and 5 (15%) patients with midshaft hypospadias (10). Kaya et al. reported 58 (77%) coronal hypospadias, 15 (20%) penile hypospadias, and 2 (3%) penoscrotal hypospadias (11). Jonuzi et al. reported the results of hypospadias repair in 31 coronal and 48 penile hypospadias patients (12). Menon et al. reported a total of 94 patients with distal hypospadias (13). Paiva et al. reported 45 (65%) patients with anterior hypospadias, 13 (19%) patients with midshaft hypospadias, and 11 (16%) patients with proximal hypospadias (14). Asgari et al. reported 126 patients with midshaft hypospadias and 56 patients with distal hypospadias (15). Rynja et al. reported 19 (16%) patients with proximal hypospadias, 12 (10%) patients with midshaft hypospadias, and 90 (74%) patients of distal hypospadias (16). Studies by de Andrade et al., McNamara et al., and Mohammadipour et al. did not specify the type of hypospadias included in their respective studies (17–19).

Efficacy of Preoperative Hormonal Stimulation in Hypospadias

There are a number of studies reporting the use of preoperative hormonal stimulation in hypospadias patients. Hormonal therapy in the selected studies included the use of various preparations of testosterone, DHT, estrogen, and hCG. Most studies show the effect of hormonal stimulation on penile length and glans circumference as well as the risk of post-operative complications.

Gorduza et al. conducted a prospective cohort study involving 300 pediatric patients with hypospadias, with 30 patients receiving hCG or testosterone therapy. The study showed that testosterone administration caused a lower number of post-operative complications such as fistula or dehiscence than the control group. The administration of hCG did not have a significant effect on the risk of postoperative complications (8). In another study, Gorduza et al. reported a randomized controlled trial involving 241 hypospadias patients receiving promestriene. The study showed no effect of promestriene versus placebo in reducing the risk of postoperative complications in hypospadias repair, including the risk of fistula formation or dehiscence (7). Kaya et al. reported that the administration of topical DHT for 3 months poses a risk of dehiscence in smaller wounds, reduces the need for reoperation, and has a better cosmetic outcome (11). A similar study by Jonuzi et al. showed that topical DHT resulted in a reduced need for reoperation compared with the control group (12). An increase in the length of the penis and the circumference or diameter of the glans has been reported in several studies using testosterone, either in topical, parenteral, or oral preparations. Casali et al. and Paiva et al. used topical testosterone propionate or topical estradiol. Paiva et al. showed that the use of testosterone and estradiol resulted in a significant increase in penile length and penis circumference compared with the control group (10, 14). Casali et al. investigated the effect of the same regimen on the epidermal thickness and type I collagen expression, both of which were found to be significantly increased compared with the control group (10). de Andrade et al. reported the use of topical testosterone propionate for 30 days, which resulted in increased serum testosterone concentrations up to 30 days post-therapy (17).

There are four studies using testosterone enanthate as a preoperative intervention. The doses used in these studies varied, but all were administered intramuscularly. Babu et al. reported that preoperative therapy with testosterone enanthate resulted in a significant increase in penile length and glans circumference in 83% of patients with fewer complications than the control group (6). A retrospective cohort run by Luo et al. also reported similar results, with significant increases in glans length and circumference after the first dose in a subset of patients, with no further doses required (9). Menon et al. and Asgari et al. used the same dose of intramuscular testosterone enanthate with different durations. Both studies showed a significant increase in penile length and glans circumference at 2 and 3 months (13, 15).

Several other testosterone preparations have also been reported in the literature regarding hormonal stimulation in hypospadias patients. Rynja et al. reported the use of combined testosterone (testosterone propionate,

phenylpropionate, isocaproate, and decanoate), both topically and intramuscularly. The study reported that the use of testosterone did not cause a significant difference in complications compared with controls (16). Chen et al. reported the use of preoperative oral testosterone undecanoate, which resulted in a significant increase in mean penile length and diameter compared with the control group. In addition, urethral stricture complications were reported to be lower in patients receiving testosterone compared with controls (20). Mohammadipour et al. reported that preoperative testosterone use resulted in a significant increase in penile length and glans diameter after the first dose, without a significant increase in subsequent doses (19).

Penile Size

In general, most of the analyzed studies reported an increase in the patient's penis size after preoperative hormonal stimulation. Significant increases in penis size were reported in six studies. Asgari et al. showed that the administration of testosterone enanthate increased the mean penile length significantly, between 22% and 36% after 3 months of therapy (15). Paiva et al. reported a significant increase in penile length and diameter in the group of patients receiving testosterone propionate, whereas an increase in penile dimension was not significant in the group of patients receiving testosterone combined with estradiol (14). A significant increase in penis size was also reported in studies by Chen et al., Menon et al., and Luo et al (6, 13, 20). Two studies by Babu et al. and Mohammadipour et al. reported an increase in penis and glans dimensions after hormonal stimulation, although these changes were not statistically significant (9, 19).

Dose and Formulation

There is no consensus about the preparation and dosage of hormonal therapy in hypospadias, and the available data are empirical studies that cannot support any one therapeutic regimen.

Preoperative DHT treatment was reported in studies by Kaya et al. and Jonuzi et al., both of whom used a 2.5% DHT gel 1–2 times per day for three months. de Andrade et al., Rynja et al., Paiva et al., Casali et al., and McNamara et al. reported the use of testosterone in topical preparations. The most widely reported topical preparations are testosterone propionate 1% (16, 18, 21), although the duration of use of topical therapy was only reported in the study by de Andrade et al. (30 days) (17). Parenteral testosterone in the included study was administered in the intramuscular preparation of testosterone enanthate. There were variations in the dose used in these studies, with three studies reporting the use of testosterone enanthate at 2 mg/kg per month (9, 13, 15) and two studies using a dose of 25 mg/month (6, 19). The duration of testosterone enanthate administration in these studies varied between 2 and 3 months. Oral testosterone undecanoate preparation with a dose of 2 mg/kg per day was reported in one study by Chen et al., with a duration of therapy of 3 months (20).

Gorduza et al. reported the combined use of hCG 1500 IU 6 times and systemic testosterone 100 mg/m2 per month for 2–6 months. In another study, Gorduza et al. used 1% promestriene cream daily for two months before surgery (7, 8).

Post-operative Complications

Asgari et al. reported that the significant postoperative complications in the treatment and control groups were urethrocutaneous fistula formation and meatal stenosis. The study showed that the complication rate was significantly lower in the hormonal stimulation group (15). The study by Rynja et al. showed no significant difference in postoperative complication rates between the hormonal stimulation and control groups, with complications being more common in patients with proximal hypospadias and patients undergoing Duckett repair procedures (16). Babu et al. reported that patients who experienced an increase in penile dimension after hormonal stimulation had a lower risk of urethrocutaneous fistula and dehiscence of the glans than the control group. The study also reported higher satisfaction levels with cosmesis in patients receiving hormonal stimulation (9). McNamara et al. showed that hormonal stimulation reduced the risk of complications by 27% in patients receiving preoperative hormonal stimulation therapy (18). Positive results were also reported by Kaya et al., who showed that transdermal

administration of testosterone reduces the risk of urethrocutaneous fistula and scar formation, and eliminates dehiscence at the surgical site (11). Jonuzi et al. also reported a reduction in the incidence of urethrocutaneous fistula and meatal stenosis in the group receiving hormonal stimulation therapy (12).

Both studies by Gorduza et al. demonstrated lower rates of fistula complications and dehiscence in patients receiving hormonal stimulation with hCG and promestriene. However, the reduced risk of complications with both hormonal therapies was not statistically significant (7, 8). Chen et al. showed that hormonal therapy significantly reduced the risk of post-operative fistula, but did not reduce the risk of strictures or diverticulum (20).

In contrast with the above studies, the study by Menon et al. showed that patients receiving hormonal stimulation experienced higher post-operative edema and inflammation than the control group. Furthermore, this condition was also associated with dehiscence in the surgical area, which in this study was only found in the group receiving hormonal stimulation (13).

Intraoperative Bleeding

The effects of preoperative hormonal stimulation on the risk of intraoperative bleeding is still largely unknown. An increased risk of intraoperative bleeding was reported in the study by Mohammadipour et al., in which intraoperative bleeding requiring the use of tourniquet occurred in 8 out of 18 patients (44%) receiving testosterone, compared with 6 out of 25 patients (26.1%) in the control group (19). On the other hand, studies by Luo et al., Chen et al., Kaya et al., and Menon et al. specifically mentioned that no intraoperative bleeding was encountered in their study population (6, 11, 13, 20). Studies by Gorduza et al., Babu et al., Casali et al., de Andrade et al., Jonuzi et al., McNamara et al., Paiva et al., Rynja et al., and Asgari et al. did not mention the risk of intraoperative bleeding in their respective studies (7–10, 12, 14–18).

Side Effects

The use of hCG and androgens in the treatment of hypospadias is generally well tolerated without significant side effects. The studies included in the analysis showed no serious adverse events, despite the risk of pubic hair growth and genital pigmentation in the studies by Paiva et al., Asgari et al., and Mohammadipour et al (14, 15, 19). de Andrade et al. reported that preoperative testosterone stimulation resulted in an increase in serum testosterone concentrations up to 30 days after discontinuation of therapy, and could result in a mild rise in systolic blood pressure (17).

Success Rates

Post-operative success rate is defined as the proportion of patients undergoing hypospadias surgery that requires no-repeat surgery for further correction. Overall, success rates appeared to be higher in patients receiving preoperative hormonal stimulation compared with the control groups in several studies. Gorduza et al. reported a 77.9% success rate in the placebo group and an 80.7% success rate in the promestriene group (7). Chen et al. reported a significantly higher success rate in the testosterone group (85.3%) compared with the control group (61.1%) (20). Jonuzi et al. reported a 90.9% success rate in the DHT group compared with a 60% success rate in the control group (12). Similar results were also reported by Kaya et al., with a 97% success rate in the DHT group and a 76% success rate in the control group (11). McNamara et al. did not report their post-operative success rates specifically, but remarked that the use of preoperative testosterone reduced the need for surgery for complications by 27% (18).

Post-operative success rates were not reported in studies by Luo et al., Gorduza et al., Babu et al., Casali et al., de Andrade et al., Mohammadipour et al., Menon et al., Paiva et al., Rynja, et al. and Asgari et al. (6, 8–10, 13–17, 19).

Conclusion

Currently, there is evidence in the literature supporting the use of preoperative hormonal stimulation in hypospadias patients. Most hypospadias cases reported in the literature were distal hypospadias, although the overall classification of hypospadias is not uniform in all studies. Hormonal therapy that has been reported to have

a significant effect on the dimensions of the phallus and the risk of complications is testosterone, both topical, intramuscular and oral preparations, and topical DHT. Doses of parenteral testosterone stimulation reported in the literature vary from 2 mg/kg per month to 25 mg/month. The recommended duration of therapy in the literature ranges from 2 to 3 months. Most studies show an increase in penis and glans size after 30 days of therapy, with the best results obtained after three months of hormonal stimulation. An increase in penis size is generally associated with a lower rate of postoperative complications, with the most common complications being urethrocutaneous fistula, surgical wound dehiscence, and meatal stenosis.

The effects of preoperative hormonal stimulation on the risk of intraoperative bleeding are still largely unknown, with a single study reporting an increased risk of bleeding, while other studies did not report any intraoperative bleeding. The administration of hormonal stimulation in hypospadias patients has a good safety profile with no reported severe side effects. Post-operative success rates are higher in hypospadias patients receiving preoperative hormonal stimulation. The results of the meta-analysis using a random effect approach showed that preoperative hormonal administration was proven to be significantly able to provide a higher average effect on penile length with no hormone administration. Overall, there is a need for high-quality empirical studies involving more samples, with standardized regimens to ensure the efficacy and safety of hormonal stimulation in hypospadias patients.

Limitation of the Study

This research has the strength of a systematic approach related to identification, selection, and extraction that has followed a systematic review data search framework to find quality sources according to the research question. The limitation found in this study is that the topic is quite complex so the search requires a high workload. Another limitation is that this analysis is based on the review authors' interpretations that are based on the main study. Major research could have provided a lot of information from some of the topics we cover.

Author contributions

All other authors contributed equally in the conceptualization and writing of the first draft to reviewing and editing the original draft.

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