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Research Article

# Use of Hormones Prior to Hypospadias Repair: A Systematic Review and Metanalysis

*Mendes de Souza MB[1,2], Passos CL[2], Correia Leite MT[3], Carvalho BCN[2], Laks M[2], Saconato H[2] and Freitas Filho LG[2,3]**

[1]Department of Pediatric Endocrinology, Hospital Santa Marcelina, Federal University of São Paulo, Brazil

[2]Postgraduate Course in Translational Medicine, Federal University of São Paulo, Paulista School of Medicine, Brazil

[3]Department of Surgery, Federal University of São Paulo, Paulista School of Medicine, Brazil

## Abstract

**Objective:** To assess whether fewer complications occur after hypospadias repair preceded by hormonal stimulation.

**Materials and methods:** Word combinations were selected for seven electronic databases and for the grey literature. The acronym "PICOS" was used in considering the eligibility of the studies to be included/excluded: humans aged 0 to 18 years with hypospadias (Population); papers in which preoperative hormone therapy was used (testosterone, dihydrotestosterone, chorionic gonadotropin and estrogen) in different degrees of hypospadias (Intervention); patients undergoing hypospadias repair with no hormonal intervention (Comparison); fewer surgical complications such as fistula, dehiscence, stenosis or urethral diverticulum (Outcomes); and randomized clinical trials (Study design).

**Results:** Search strategy came to 5.461 references altogether. Eight papers were included for qualitative synthesis. There is good evidence that a 2 mg/kg testosterone dose through the intramuscular, topic or oral routes, favors penile enlargement. The most frequent complications were uretrocutaneous fistulas (42%) and glans sutures dehiscence (25.2%).

**Conclusions:** Metanalysis showed fewer chances for uretrocutaneous fistula in the group that received androgen. For further complications the use of hormone prior to hypospadias repair showed no difference between the experimental and control groups. Intramuscular or topical testosterone, in a 2 mg/kg dose, showed to be effective for penile enlargement and it should be considered in hypospadias with small glans and/or little developed prepuces. With respect to estrogen, few papers have been published on penile tissue, making it impossible to reach any conclusion.

**Keywords: Hypospadias; Hormone; Systematic review; Metanalysis surgery**

## Introduction

Hypospadias is a most common congenital anomaly that affects the external genital organs of male, i.e., about 1 in every 250 live newborns [1,2]. The etiology of hypospadias remains unknown, and most cases fail to have a unanimously accepted explanation [1]. The abnormal genital development may result from insufficient testosterone synthesis, inappropriate conversion of testosterone into dihydrotestosterone, inappropriate Androgen Receptor (AR) levels or reduced AR gene expression, less or absent AR protein activity or abnormal receptor response resulting in androgen insensitivity conditions [3].

The phenotypic classification of hypospadias seeks to assess the severity of its three main components: urethral meatus location, ventral penile curvature degree ("chordee") and soft tissues morphology of the external genital organs. Degree of the ventral penile curvature, abundance or lack of local skin and the urethral plate condition can add to the complexity and, thus, directly influence the surgical approach and risk for potential complications [4,5].

Hormone therapy prior to surgical repair of hypospadias was first described in 1971 [6]. Testosterone binds to the androgen receptor, and it also acts on tissues that express the 5alpharedutase enzyme, converting into dihydrotestosterone that binds more eagerly to the androgen receptor as compared to testosterone, acting on the external genitalia [7]. Preoperative hormone stimulation with androgen aims to promote penile enlargement and augmented glans diameter, facilitating reconstruction of a new urethra, besides improving the local vascularization, resulting in a more proper healing [8-13].

Estrogen receptors were found in the glans and prepuce of children with hypospadias, and they may modulate healing, as they increase the deposition of collagen and reduce the inflow of inflammatory cells. Preoperative topical estradiol is believed to increase resistance to traction of the penile tissue in boys with hypospadias, improving wound healing [13-17].

Despite no sufficient evidence supporting the benefits of hormone use in reconstructive hypospadias surgery, the papers published show controversial postoperative observations. More investigations are required to assess pros and cons. In this systematic review with metanalysis and better evidence, we intend to assess if there are fewer complications in the surgical repair of hypospadias following hormone stimulation, and thus, to verify, the most suitable type of

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***Corresponding author:** Luiz G Freitas Filho, Department of Surgery, Postgraduate Course in Translational Medicine, Federal University of São Paulo, Paulista School of Medicine, Rua Batista Cepelos 87 - ap 61, 04109-120 São Paulo, Brazil, Tel: +55 11 983231299

hormonal stimulation, the best dose and the administration route to be used in the preoperative period of patients with hypospadias.

## Materials and Methods

The protocol of this systematic review was registered with the PROSPERO Website (International prospective register of systematic review - Center of Reviews and Disclosure University of York) - CRD42022347975, and the review complied with The PRISMA 2020 Statement: an updated guideline for reporting systematic reviews [18].

### Eligibility criterion

To consider the eligibility of the studies to be included in or excluded from this review, the acronym "PICOS" was employed to answer the following focused question: "Are there fewer complications in hypospadias repair following hormone therapy?":

Population (P): participants aged from zero to 18 years with different forms of hypospadias.

Intervention (I): papers in which the intervention was preoperative hormone therapy (testosterone, dihydrotestosterone, chorionic gonadotropin and estrogen) for different degrees of hypospadias.

Comparison (C): patients undergoing surgical repair of hypospadias with no preoperative hormone intervention.

Outcomes (O): the outcomes were clinically assessed by qualitative and quantitative data. Positive postoperative clinical response included fewer surgical complications such as fistula, dehiscence, stenosis and urethral diverticulum.

Study Design (S): clinical trials exclusively randomized were included. The following were excluded: non-randomized clinical trials, experimental trials or pseudo-randomized clinical trials, observational, retrospective and transversal trials, "experts" opinions, comments, letters, editorials, conference summaries, case reports and case series. There were no exclusion criteria concerning the language or date of publication of the study.

### Information sources and search strategy

Word combinations and proper truncations were selected and adapted specifically to each electronic database: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/MEDLINE, EMBASE, Scopus, Web of Science, Livivo, Latin American and Caribbean Literature on Health Sciences (LILACS).

Database searches were carried out on a single day. A second search was made at the end of the review for updates. The search in the grey literature of Google Scholar, ProQuest and medRxiv took place on the same day as the database search. No study based on the publication status was excluded while the entire paper was available. References were managed by using a proper software (EndNote® X7 Thomson Reuters, Philadelphia, PA) and all duplicate studies were removed.

With support from a librarian, the reference lists of the eligible Randomized Clinical Trials (RCTs) and further systematic reviews connected with the surgical repair were reviewed, while any further potentially eligible study not previously identified by the electronic system was determined. An expert, who did not take part in the paper's selection process, was consulted to indicate papers with potential for inclusion.

### Studies selection process

The papers were selected in two phases, with the total result of the records retrieved through the search strategy, while both independent reviewers read all references. Kappa coefficient of concordance was estimated to calibrate the selection of articles. Reading was not started until a >0.8 concordance value was achieved. In the first phase, titles and abstracts of all records retrieved through the electronic search were independently examined, identifying the randomized clinical trial relevant to the inclusion criteria. Then, any discrepancies were resolved by consultation to a third reviewer to reach a consensus and determine the article's eligibility, which ensured that all relevant studies were included with no personal bias. Articles failing to meet the eligibility criteria were excluded in this phase.

The second phase consisted of independent reading of the full text of the articles selected in the first phase. In order to protect the reading of references and ensure independence and confidentiality in both phases, the selection was managed by the Rayyan Intelligent Systematic (http://rayyan.qcri.org) tool, when the reviewers were masked in all phases and a team member, who had not taken part in the selection, acted as the moderator. The review and final selection always considered the full publication.

### Data collection process

A form was developed to standardize the data extraction, registering the relevant information, studying the characteristics of each eligible randomized clinical trial. Two reviewers independently extracted and registered in duplicate the data from every study.

Whenever a study was not found in full, or if failing to present data, three attempts were made within a 1-month interval before entering in contact by e-mail with the corresponding author. In case of no reply, the article was excluded.

### Assessment of risk of bias in the studies included

Both reviewers in charge of the independent extraction of data from the eligible randomized clinical trials also used the data collection form to assess the risk of bias in the studies included.

For randomized controlled trials, the "Cochrane's collaboration tool for risk of bias" was used, involving seven domains: generation of random sequence, occultation of allocation, blinding of participant and personnel, masking of outcome assessment, incomplete result, reports on selective results and further bias sources [19]. Each domain was classified as "high risk", "small risk" of bias or "uncertain".

### Measures of effect

Considering that the outcome selected was binary, the number of events for each group was collected and the sample size of each group was included. The relative risk was estimated between the comparison groups to be used, with 95% confidence intervals.

### Data synthesis

A randomized effects metanalysis method was carried out through the statistical software RStudio version 1.2.1335 (Rstudio Inc, Boston, EUA), with the studies weighted by the Mantel Haenszel method. Heterogeneity was estimated by the inconsistency index ($I^2$) and variance by $Tau^2$, estimated by the DerSimonianLaird method. 95% confidence intervals were generated (CI 95%) and the level of significance was established at 5%. For metanalysis, a minimum number of three articles was set with the required data that met the eligibility criteria.

### Analysis of certainty of evidence

The level of certainty of evidence was assessed by using

classification for recommendations, development, and evaluation (GRADE) [20]. It classified the certainty of evidence into four levels: very small, small, moderate, and high. This tool considers five aspects to classify the certainty of evidence: methodological limitations (bias risk), inconsistency, indirect evidence, inaccuracy, and publication bias.

## Results

### Study selection

The search strategy retrieved 5.461 references from the seven electronic databases, 2.976 of which remained after duplicate articles were excluded. After the titles and abstracts were read (phase 1), 15 articles were selected to be read in full (phase 2), 8 of which were excluded (Figure 1). One hundred and seventy four (174) articles were found while consulting the grey literature, with one paper indicated by an expert. Eight articles were selected for qualitative synthesis (Figure 1). Kappa concordance coefficient value was >0.8 for both pairs, which indicates excellent agreement between the first and the second reviewers.

### Studies characteristics

This systematic review included eight studies, published between 2007 and 2023, in the English language, from Iran, China, France, Egypt, Turkey/Austria and 3 articles from India. All studies were classified as randomized clinical trials (Table 1) [10,2127].

### Participants

Nine hundred and twenty-three (923) patients from the eight studies included were analyzed, 462 (50%) of whom received some kind of hormone therapy. Age range among all patients involved varied from 6 months to 12 years, while most studies were conducted in the preschool phase, age up to 3 years (Table 1). Just one paper included adolescents aged up to 12 years [23].

As for the type of hypospadias, from the seven papers assessed, four hundred and sixty-three patients had distal hypospadias, two hundred and ninety-four had midshaft and one hundred and fifty and one had proximal hypospadias. Wali et al. [24] omitted such information. The number of participants is proportional between the experimental and control groups.

### Adverse hormonal effects

As for adverse hormonal effects, all authors reported as being discreet and transitory. Wali et al. alone, who used topical testosterone, mentioned nothing about the occurrence of side effects [24]. Genital darkening and appearance of pubic hair were the most frequent findings [2224,27]. In the intramuscular application of testosterone all patients had genital hyperpigmentation in Asgari et al. [22] study and 15.4% of the children developed scarce pubic hair that disappeared three months after the use. Babu et al. reported the presence of pubic hair in 6.4% of the patients in the group that had more than two mm penile enlargement [26]. Menon et al. [23] referred to increased erythema and edema in the first change of bandage on the fifth postoperative day and then for another 2 weeks, which was not found in patients in the control group. Chen et al. [21], that used orally administered testosterone, found no adverse effect connected with the hormone. Kaya et al. [9] that prescribed topical dihydrotestosterone, reported itching, darkening of the skin and erythema in thirteen (18%) out of their thirty-seven patients. All effects mentioned disappeared after two weeks of use [10].

Out of the two hundred and thirty patients in Gorduza et al. [25] paper, one hundred and fourteen used preoperative estrogen and as few as nineteen (8.2%) had some kind of adverse effect. The authors report as expected events the appearance of erythema in seventeen (14.9%) children in the estrogen group and in twenty-four (20.6%) in the placebo group, besides gynecomasty in as few as two patients that received estrogen and one patient in the placebo group. All effects were temporary [26]. In Pati et al. [27] paper, one patient in the estrogen group who developed rashes following the initial application of estriol cream was excluded from the project. No patient presented adverse effects such as genital pigmentation or gynecomasty during the study period [28].

Chen et al. after using hormone for 1 year reported that there was no advance in bone age through the treatment duration and dose presented [21]. Gorduza et al. [25] mentioned that the mean difference in bone age was not statistically different between the estrogen and placebo groups. Asgari et al. [22] although not mentioning the bone age, described that the mean height of the patients at the beginning of the study was 91.6 cm in the experimental group and 88.7 cm in the control group. It accelerated after three months of therapy to 92.8 cm in the hormone group and 89.8 cm in the control group.

### Hormone dosages

In Asgari et al. [22] study, basal serum testosterone levels were mean 46 ng/dl in the study group and 47 ng/dl in the control group. During the testosterone therapy, levels increased significantly reaching a 462 ng/dl peak in the intraoperative (4 weeks following the second injection). For twelve children in the experimental group, serum concentrations of testosterone reached quite high levels (>1000 ng/dl). Three months after the therapy ended, the values fell back close to the basal level.

Chen et al. [21] referred that the serum level of testosterone following the use of hormone was significantly higher than in the pretreatment; however, still remaining within the normal range for prepubescent (0-20 ng/dl); on the other hand, FSH and LH serum levels were not significantly different before and after the hormone. Serum testosterone returned to the pre-treatment level just 1 month after the therapy was completed. In the study by Gorduza et al. [25], LH, FSH and estradiol mean values did not differ between the placebo and promestriene groups.

The basal level of serum testosterone in Menon et al. paper was normal for the age in all groups and after three hormone doses it rose to an average of 32.98 ± 20,57 ng/dl in the group that underwent surgery after 1 month of the injection and to 32.10 ± 21,21 ng/dl in the group undergoing surgery after 3 months. In the intraoperative of 3 months of therapy, the level fell to 2.16 ± 4.32 ng/dl. The mean level of serum testosterone was 32.05 ± 21.59 ng/dl for boys aged under 5 years as compared to 16.68 ± 22,07 ng/dl for the ones aged over 5 years [23]. The further studies did not assess hormone serum levels [10,24,26,27].

### Postoperative complications

Nine hundred and twenty-three participants were computed from the eight papers included, two hundred and thirty-four (25.3%) of whom were found to have had some kind of postoperative complication, ninety-seven (41.5%) in the group receiving hormone therapy and one hundred and thirty-seven (58.5%) in the control group (Table 1).

Ureterocutaneous fistula was the most frequent complication,

in ninety eight patients altogether (42%), thirty-seven in the group receiving hormone treatment (testosterone twenty-one, estrogen fifteen and dihydrotestosterone one) and sixty-one in the control group. In Gorduza et al. [25] study, thirtysix boys had at least either one urethral fistula or urethral dehiscence during the first year following the surgery. The exact numbers of such events were clear in only ten children, six of which in the placebo group and four who received topical estrogen.

Glans dehiscence occurred in fifty-nine (25.2%) participants, thirty-two of whom in the control group and twenty-seven that used hormone (testosterone fifteen and estrogen twelve). In the group treated with dihydrotestosterone, no patient had glans dehiscence [10]. Whereas urethral suture dehiscence was reported only in Gorduza et al. [25] paper, with ten (4.3%) patients, six in the placebo group and four who had topical estrogen (Table 1).

Meatal stenosis appeared in twenty-four (10.2%) participants, thirteen of whom used testosterone and eleven in the control group. Papers by Kaya et al. [9], Menon et al. [23], Gorduza et al. [25], and Pati et al. [27] mentioned no such complication. Urethral stenosis was reported in nine (3.8%) children, five in the control group, and four in the group undergoing estrogen, no patient using testosterone developed such complication [9,21,27].

Seven children had urethral diverticulum (3%), three of whom in the group that used testosterone, four in the control group and none in the group treated with dihydrotestosterone [21,22]. Kaya et al. [9] reported high rates of hypertrophic scars in eighteen (7.7%) patients, two of whom used dihydrotestosterone and sixteen in the control group. Wali et al. [24] reported the presence of edema in nine (3.8%) participants, seven who used testosterone and two in the control group.

### Risk of bias in the study

Out of the eight randomized clinical trials, three presented over 80% of their domains classified as low risk of bias [22,25,27]. Three studies were classified as being of moderate risk of bias [9,23,24]. Two presented 33.3% of their domains with high risk and 50% with low risk of bias (Figure 2) [21,26]. Among the studies, performance bias was the most deficient domain with blind participants and personnel.

### Synthesis results

Eight papers underwent quantitative synthesis, with effect metanalysis conducted showing the following outcomes: urethrocutaneous fistula, glans dehiscence, meatal stenosis and urethral stenosis. When comparing the risk for urethrocutaneous fistula among the ones who used hormone and the control group, a relative risk difference was found in the experimental group on androgen (RR = 0.59; CI 95% = 0.35-0.97; I2 = 0%), showing less chances for fistula in the group that received androgen. In the subgroup on estrogen, the trials showed no statistically significant difference (RR = 0.72; CI 95% = 0.43–1.22; I2 = 0%). In this result the studies showed no heterogeneity (Figure 3A).

The global relative risk of glans dehiscence presented small heterogeneity among the clinical trials; and metanalysis showed no statistically significant difference between the experimental and control groups (RR = 0.77; CI 95% = 0.39 –1.54; I2 = 25%) (Figure 3B). Heterogeneity occurred in Menon et al. paper, the only study to include adolescents, assigning the risk for dehiscence to an increased inflammatory reaction and edema on the fifth postoperative day, which was not reported in the control group patients [23].

No statistically significant difference was found in meatal stenosis with homogeneous studies (RR = 1.22; CI 95% = 0.55–2.71; I2 = 0%) (Figure 3C).

A moderate degree of heterogeneity was identified in urethral stenosis among the studies (I2 = 60%; Tau 2 = 3.3115; p = 0.08). Such inconsistency occurred in Pati et al. [27] study, the only randomized clinical trial in which the patients included had already undergone a first stage urethroplasty. The global relative risk showed no statistically significant difference between the experimental and control groups (RR = 0.68; CI 95% = 0.05–9.81; I2 = 60%) (Figure 3D).

### Certainty of evidence

The certainty of evidence assessed by the GRADE tool was considered low for all outcomes analyzed. The main factors for less certainty of evidence were methodological limitations, generating a potential risk for bias, and inaccuracy, considered severe in all analyses (wide confidence interval) (Figure 2).

## Discussion

This review aimed to go over the different papers that assessed the effects of preoperative use of hormones for patients undergoing surgical repair of hypospadias. Androgens have been used to improve postoperative results. They are believed to offer an anatomic condition that lessens the surgeon's technical limitation such as larger glans diameter, improved urethral plate, penile curvature and prepuce volume, and also that they may cause increased vascularization and as a result, improved healing. However, there is no consensus on how useful the use of those hormones would actually be.

There seems to be good evidence that the use of intramuscular, topical or even oral testosterone, favors enlargement of the penis, although it is not clear whether there is an actual improvement in postsurgical outcomes from hormone use [10]. In this systematic review eight studies were assessed, five of which using testosterone, three intramuscularly, one orally and one topical. In all five studies, the doses and length of use were similar and all showed good response in increased penile length. However, results differed in relation to a possible reduction in postoperative complications.

Different authors claimed to fear using preoperative androgens as the increased vascularization could cause edema or erythema, thus compromising healing and increasing the risk of bleeding during the surgery [28]. Bastos et al. [11], however advocated that a properly nourished and oxygenated skin, for having greater blood flow, can lessen fibrosis and, therefore, tend towards better healing, which would result in a smaller probability of postsurgical complications. With this in mind, they studied the histological findings observed in the prepuce, following application of topical testosterone in twentysix children with hypospadias. They noticed increased tissue vascularization, however, failed to mention whether there were improved final results from the treatment.

In relation to adverse effects of androgens, Heinrich et al. [29] report that a possible disadvantage of topical application can be that it may lead to uncontrolled absorption, with possible and undesirable side effects such as strong masculinization, growth acceleration and skeletal maturation. In fact, they mention in the study a slightly accelerated bone growth that was temporary in seven of the nine children. In three children pubic and axillary hair appeared. Tsur et al. [30] refer that with treatment restricted to a few months such

effects seem to be transitory. It can be said that in all of the six papers included in this systematic review, adverse effects of testosterone were minimal and transitory.

Although the exogenous administration of sexual steroids accelerates epiphyseal maturation, most studies indicate that a careful treatment with low doses of testosterone and of limited duration, for up to 6 months, can be used with no side effects for the projected final height [3133]. In this review only two studies assessed the bone age and neither showed any advance in the treatment duration or dose [21,25]. The hormone serum measures brought nothing new.

Wright et al. [33], in 2013, conducted the first systematic review with metanalysis, in an attempt to assess the effect of androgen administered prior to surgical repair of hypospadias. Eleven (11) papers (622 patients) were included. Most of those studies were observational and retrospective, of moderate or poor quality. Of the patients, 45% were administered hormone, with intramuscular testosterone being the most commonly formulation prescribed. As few as four studies (36%) approached postsurgical complications and were included in metanalysis. The results of this analysis suggest a possible relationship between the use of hormone and increased complication rates in patients with more severe cases of hypospadias. Given the subjectivity involved in the selection of patients for hormone administration, it may have included patients with a more severe anatomic defect or presenting more unfavourable tissue characteristics and who, as a result, would present greater risk of complications. Therefore, these findings must be carefully interpreted, and it cannot be clearly stated that a relationship exists between the use of hormone and a greater number of postsurgical complications.

In 2017, Chua et al. [34] conducted a systematic review on the matter using twelve papers. In nine cohort studies with moderate to high risk of bias for patient selection no significant difference was found in the postsurgical outcomes with or without the use of hormone. Whereas when assessing the metanalysis of three randomized clinical trials with better quality of evidences, a significant reduction was found in post-surgical complications, such as uretrocutaneous fistulas and need for new surgical approaches. Those three RCTs were eligible and used in this review.

In the last systematic review on the issue published in 2023 by Do MT et al. [35], thirtytwo studies were selected, including randomized and non-randomized clinical trials. Assessment of the administration route showed the intramuscular effect not to differ from topical or oral use. Post-surgical rate of complications was assessed in 14 studies available for metanalysis, 5 of which were randomized control trials and 9 non-randomized - the latter with over half the risk of bias considered severe. Although the treatment had no effect on the overall rate of complications (RR=1.08; CI 95%= 0.75 – 1.54; I2 =80.95%), the postsurgery risk of uretrocutaneous fistula (most common complications) was smaller in those receiving preoperative testosterone than in the controls (RR=0.62; CI 95%= 0.41–0.93; I2 =0%) [35]. All five randomized clinical trials were eligible and used in this review. In this systematic review using only randomized clinical trials, patients preoperatively receiving androgen had a smaller rate of uretrocutaneous fistula, with metanalysis showing a difference in relation to the relative risk in the experimental group with androgen. Although glans dehiscence rates were smaller in the experimental groups, metanalysis showed no significant difference in the use of hormone in the further postoperative complications.

Menon et al. was the only one to report significantly greater complications in the group on testosterone and to include adolescents aged up to 12 years, attributing the risk of glans dehiscence to a greater inflammatory reaction on the fifth postoperative day, which was not noticed in the control group.

In the recent years an increased interest has been noticed in preoperative therapy using estrogens to improve surgical outcomes in patients with hypospadias. There is evidence that the endogenous effect of estrogens promotes faster healing, increase penile vascularization and prompt increased collagen prior to hypospadias repair, while restricting the magnitude of the local inflammatory response [16].

Paiva et al. assessed the measures of hypospadias penis after hormone therapy using topical testosterone and estrogen, few side effects occurred following the use of either hormones, all transitory and improving after ninety days [17]. In Gorduza et al. [25] study the surgical procedure was carried out one day after the last dose of estrogen, leading us to believe that it failed to reach its full result. The benefits from its use are not conclusive; therefore, more studies are required.

The certainty of evidence assessed by GRADE was considered low for all results analyzed, so, metanalysis results were inaccurate in assessing the use of hormone prior to hypospadias repair to lessen postsurgical complications. The papers studied present factors of confusion with conflicting protocols for hormone stimulation, classification of hypospadias and heterogeneous surgical techniques, generating bias and reducing the certainty of evidence.

## Conclusion

Metanalysis showed reduced chances for uretrocutaneous fistula in the group on androgen. In the further complications, the use of hormone prior to hypospadias repair presented no difference in the risks between the experimental and control groups. Intramuscular or topical 2 mg/kg testosterone, showed to be effective for penile increase, and it should be considered in hypospadias with very small glans and/or poorly developed prepuces. As for estrogen, few papers on penile tissue have been published, making it impossible to reach any conclusion.

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**Table 1:** Characteristics of the included studies.

| Study, Author / Year / Country | Study design | Participants | Intervention | Outcomes measures | Results | Conclusions |
|---|---|---|---|---|---|---|
| Asghar et al., 2015 Irã | Randomized Clinical Trial | N = 182, 168 completed, 6 dropped out in Group 1 and 8 in Group 2 ID = 18 - 52 m | Testosterone enanthate: 2 doses: 2 mg/kg/dose. IM, for 2 months before surgery. | FU: T:4, C:7 | The overall complication rates in Group 1 (5.5%) were significantly lower compared to Group 2 (13.2%) (p=0.03). The overall complication rates for both groups were as follows: urethrocutaenous fistula 0.04%, metal stenosis 2.1%, wound dehiscence 0.54%, and urethral diverticulum 0.54%. | Parenteral administration of testosterone prior to hypospadias repair is beneficial in decreasing complication rates. |
| | | | Surgical techniques: TIP | DG: T:0, C:1 | | |
| | | 2 Group: Group 1(n=85) Testosterone; Group 2(n=83) Control | Surgery: 4 weeks after last dose | EM: T:1, C:3 | | |
| | | | Follow-up: 2 years | DU: T:0, C:1 | | |
| Babu et al, 2018 India | Randomized Clinical Trial | N = 200, 188 participated, 6 in Group 1 and 8 dropped out in Group 2 ID = 12 - 15 m | Testosterone enanthate: 3 doses: 2 mg/kg/dose, IM, at 10 and 11 m of age. | FU: C: 7, T1a: 2, T1b: 4 | Total complications were significantly lower in the T1b group (17.9%) than in the T1a group (50%). The reoperation rate was significantly lower in group T1b (11.5%) than in group 2 (23.1%). | Preoperative testosterone increases the width of the glans, thus reducing complications and the need for reoperation. It also improves cosmetic results and satisfaction. Although the rate of urethrocutaenous fistula was lower in the T1b group, this did not reach statistical significance as the numbers were small. Glans dehiscence was common in group 2, which did not receive testosterone. Glans dehiscence was the cause of glans fistula in groups 2 and T1a due to the small diameter of the glans. |
| | | | Subdivided: Group T1a: 16 did not respond to phallic enlargement above 2 mm | DG: C: 13, T1a: 4, T1b: 3 | | |
| | | | Group T1b: 78 responded | EM: c: 6, T1a: 2, T1b: 7 | | |
| | | 2 Group: Group 1(n=94) Testosterone; Group 2(n=92) Control | Surgical techniques: TIP | DU: T: 0, C:0 | | |
| | | | Surgery: timing was unclear | R: C: 22, T1a: 5, T1b: 9 | | |
| | | | Follow-up time: 1.5 years | | | |
| Chen et al. 2015 China | Randomized Clinical Trial | N = 72, 70 participated, 2 excluded in Group 1 ID=21.6 ± 15.7 m | Testosterone undecanoate: 2 mg/kg/day, orally, with a maximum dose of 120 mg/day. Doses ranged from 10 to 40 mg/day. | FU: T: 2, C: 9 | Average penis length and diameter increased by 1.06 ± 0.53 cm and 0.30 ± 0.009 cm. Postoperative complications included fistulas in 9 patients (25%) in group 2 compared to 2 (5.9%) in group 1. While 3 (8.3%) in group 2 had urethral strictures none in the testosterone group had this complication. There were three (8.3%) Children with diverticula in group 2 and three (8.9%) patients with this complication in group 1. No patient had EM, DG or residual cord in either group. There was an important difference between the reoperation rates of group 2 (14, 38.9%) and group 1 (5, 14.7%). | Oral testosterone undecanoate therapy prior to hypospadias repair is beneficial in children with microphallic hypospadias. Significant penile growth was observed in children treated with limiting. Furthermore, undecanoate is beneficial in decreasing complication and reoperation rates of hypospadias repair. |
| | | | 26 boys turned 3 months old. | DG: T: 0, C: 0 | | |
| | | | 8 completed 6 months. | EU: T: 0, C: 3 | | |
| | | 2 Group: Group 1 (n=34) Testosterone; Group 2 (n=36) Control | Surgical techniques: Duckett: 62; Duckett and Thiersch-Duplay: 8 | DU: T: 3, C: 3 | | |
| | | | Surgery: 3 to 6 months after last hormonal dose. | EM: T: 0, C: 0 | | |
| | | | Follow-up time: 3.5 years. | R: T: 5, C: 14 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Godruza et al., 2020 France | Randomized Clinical Trial | N = 241, 230 participated, 5 excluded in Group 1 and 6 in Group 2. ID= 9-36 m | Promtestriene 1%: topical for 2 months before surgery. | FU or DIU: 38 at least one complication P: 19, E: 7. | Of the 241 patients, 122 were randomized to placebo and 119 to Promestriene. The primary outcome was not available for 11 patients. Healing complications were assessed at 16.4% (19/116) on placebo versus 14.9% (17/114) on promestriene and the center-adjusted probability was 0.93[0.45; 1.94] (p=0.86). | Although we observed a lower overall risk of complications compared to previous publications, postoperative complications were not different between promestriene and placebo due to lack of study power or ineffectiveness of promestriene. The present study demonstrated no effect of promestriene versus placebo in reducing postoperative complications of hypospadias. |
| | | | Surgical techniques: ONLY: 230. | | | |
| | | 2 Group: Group 1 (n=114) Estrogen; Group 2 (n=116) Placebo | Surgery: 1 day after last hormonal dose. | FU and DIU: presence of two complications P: 6, E: 4. | | |
| | | | Follow-up time: 1 year. | | | |
| Kaya et al., 2007 Turkey Austria | Randomized Clinical Trial | N= 75 ID= 33.4 ± 3.7 m | Dihydrotestosterone (DHT) gel 2.5%, topical, Dose 0.2 to 0.3 mg/kg, once a day for 3 months. | FU: DHT: 1, C: 4 | Postoperative complications included FU in 4 patients (11%) in group 2 compared with 1 (3%) in group 1. While 3 patients (8%) in group 2 experienced DG, no patients in the DHT group experienced this complication. There were 2 with EM in group 2 (5%) and none in group 1. Additionally, there were 16 (42%) with high rates of hypertrophic scanning in group 2, compared to 2 (5%) in the dihydrotestosterone group. There was a significant difference between the overall reoperation rates of group 2 (9 patients, 24%) and group 1 (1 patient, 3%, p<0.05). None showed signs or symptoms or symptoms of EU or diverticulum. | Pretreatment with transdermal dihydrotestosterone gel was effective in reducing complications and improving aesthetic results after hypospadias repair. |
| | | | | DG: DHT: 0, C: 3 | | |
| | | | Surgical techniques: TIP | EU: DHT: 0, C: 2 | | |
| | | 2 Groups: Group 1 (n=37), DHT; Group 2 (n=38) Control. | Surgery: 5 weeks after last hormonal dose. | DU: DHT: 0, c: 0 | | |
| | | | | R: DHT: 1, C: 9 | | |
| | | | Follow-up time: 1 year | Scar: DHT: 2, c: 16 | | |
| Menon et al., 2017 India | Randomized Clinical Trial | N=94 ID: 1 to 12 years old | Testosterone enanthate 3 doses: 2 mg/kg/dose, 1M, 1 month apart. | FU: C: 7, T: 5 | 94 patients underwent urethroplasty over a period of 3.5 years. Penile dimensions increased significantly after testosterone use. Group 1 patients tented to have more postoperative edema and inflammation, although FU rates were similar in Group 2 (n=7) and Group 1 (n=5), glans dehiscence occurred only in Group 1. | Testosterone should be used judiciously in distal hypospadias. While tissue availability increased significantly, there was an increase in the inflammatory reaction and edema, which increased the risk of wound dehiscence in cases of early surgery. |
| | | | | Group T1a: 2 | | |
| | | | Surgical techniques: TIP: 84; ONLAY: 2; Mathieu: 4; Thiersch Duplay: 4 | Group T1b: 3 | | |
| | | 2 Groups: Group 1 (n=49) Testosterone, Group 1a (n=23) Group 1b (n=26); Group 2 (n=45) Control | Surgery subdivided: Group 1a operated 1 month after injection. Group 1b: operated 3 months after injection. | DIG: C: 0, T: 7 | | |
| | | | | Group T1a: 3 | | |
| | | | Follow-up time: 1.5 years. | Group T1b: 4 | | |
| Pati et al., 2023 India | Randomized Clinical Trial | N=64, 60 participated, 1 excluded in the Placebo Group and 3 in the Estrogen Group ID= 2 to 9 years | Estriol 0.5 mg: topical, Once a day for 30 days. | FU: E: 11, P: 16 | Postoperative complications were not significantly different in the estrogen group (44.8%) compared to the placebo group (51.6%). Urethrocutaneous fistula occurred in 51.6% of patients in the placebo group compared to 37.9% in the estrogen group. Glans dehiscence occurred in 12 estrogen patients compared to 14 in the placebo group. Four patients developed urethral strictures during follow-up in the estrogen group. | Application of estrogen to proximal hypospadias before surgery did not reduce the incidence of common complications associated with repair (fistula and glans dehiscence). |
| | | | Surgical techniques: TIP | DG: E: 12, P: 14 | | |
| | | 2 Groups: Group 1 Estrogen (n=29); Group 2 Placebo (n=31) | Surgery: 1 month after last hormonal dose. | EU: E: 4, P: 0 | | |
| | | | Follow-up time: 2 years. | | | |
| Wali et al., 2020 Egito | Randomized Clinical Trial | N=40 ID: 6 m to 3 years | Testosterone gel 1%: topical once a day for 30 to 40 days. | FU: T: 4, C: 5 | Significant increase in all penile parameters after hormonal stimulation in group 1. Ventral length of the penis distal to the meatus showed greater growth compared to the ventral length of the penis proximal to the meatus, denoting disproportionate penile growth. We found no significant difference between the two groups in terms of the rate of postoperative complications. | The use of preoperative topical testosterone significantly increases the size of the hypospsdic phallus. However, this increase in size appears to be disproportionate on the ventral penile surface and was not reflected in improved surgical results. |
| | | | Surgical techniques: TIP 31; Two-stage repair: 9. | DG: T: 1, C: 1 | | |
| | | 2 Groups: Group 1 (n=20) Testosterone; Group 2(n=20) Control | Surgery: 1 month after last hormonal dose. | EM: T: 3, C: 2 | | |
| | | | Follow-up time: 2 years. | Edema: T: 7, C: 2 | | |

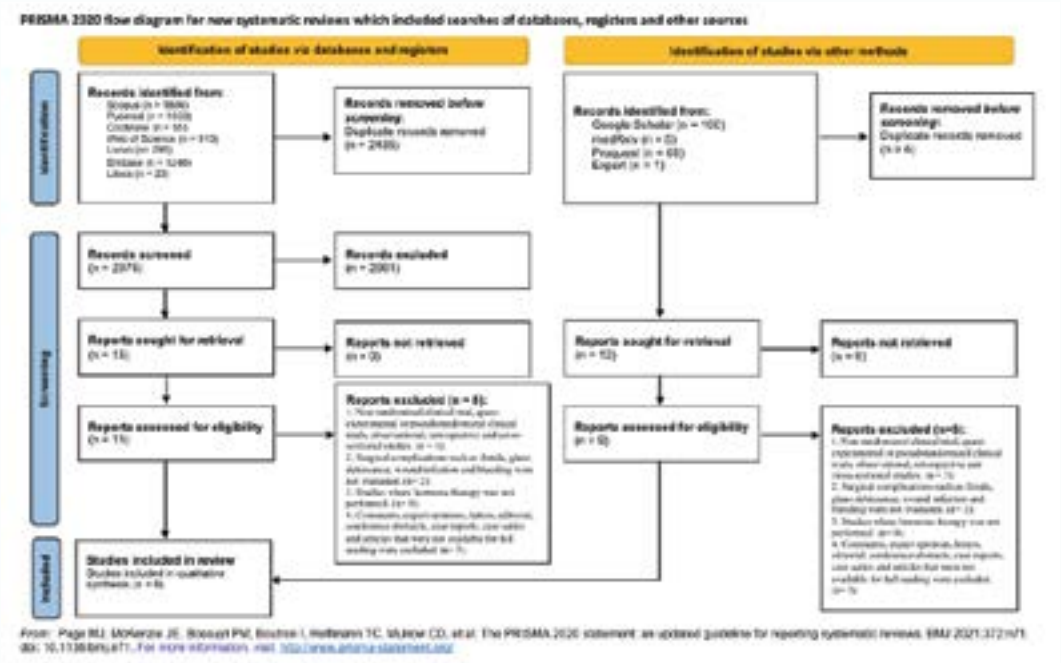


**Figure 1**: Flowchart of literature search and selection criteria.

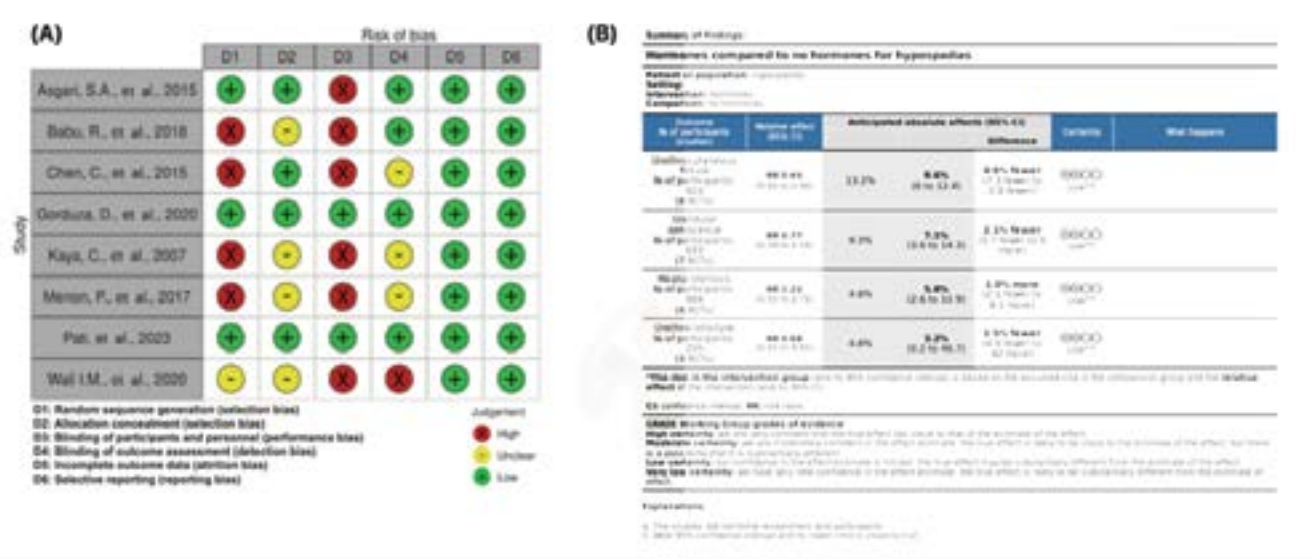


**Figure 2**: A): Summary of Risk of Bias; B): Certainty of evidence (GRADE).

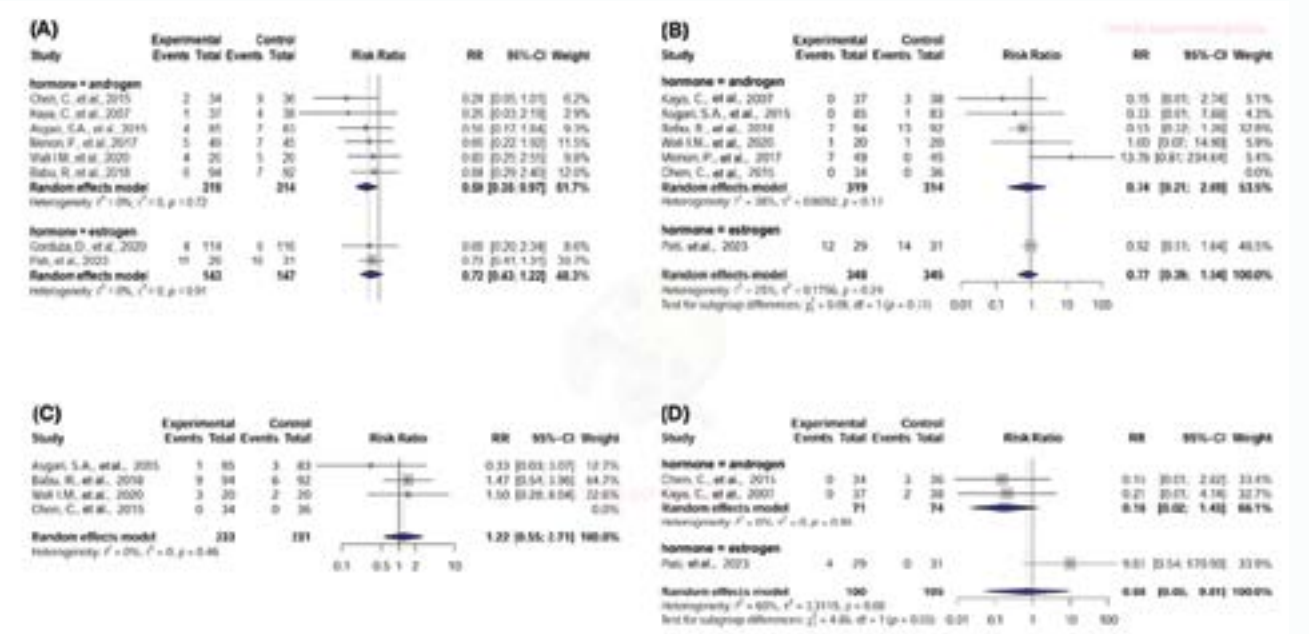


**Figure 3**: A): Forest plot chart to assess the risk of urethrocutaneous fistula; B): Forest plot chart to assess the risk of glans dehiscence; C): Forest plot chart to assess the risk of meatal stenosis; D): Forest plot chart to assess the risk of urethral stenosis.