Ph.D. Dissertation of Medicine

Effect of Preoperative Androgen Stimulation on Penile Size and Postoperative Complication Rate in Patients with Hypospadias: A Systematic Review and Meta-analysis

수술 전 안드로겐 자극이 요도하열 환자의 음경 크기 및 수술 후 합병증 발생률에 미치는 영향: 체계적인 문헌 고찰 및 메타 분석

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Abstract

Purpose: To systematically review and evaluate the beneficial effects of preoperative androgen stimulation (PAS) on penile length, glans width, and postoperative complications in patients with hypospadias using meta-analysis.

Materials and Methods: A comprehensive search of the published literature between 1980 and 2022 was done on Pubmed, Embase, Google Scholar, Scopus, Web of Science, and Proquest. Studies of patients with 5-alpha reductase deficiency, differentiation sex disorder, or micro-penis without hypospadias were excluded. The full-text screening, quality assessment, and data acquisition were done independently by two reviewers. Meta-analysis was done to quantify the penile growth and postoperative complications.

Results: The initial literature search yielded 2,389 records, wherein 32 studies were eligible for the systematic review and meta-analysis. Preoperative testosterone stimulation increased the penile length and glans width by 9.34 mm (95% CI: 6.71-11.97) and 3.26 mm (95% CI: 2.50-4.02), respectively. A longer penis at the baseline led to greater length gain following treatment (1 mm longer at the baseline was likely to gain 0.5 mm more). However, the increase in penile length was not associated with the severity of

hypospadias. While the treatment did not affect the overall complication rate, the postoperative fistula risk was lower in those receiving PAS (RR = 0.52, 95% CI: 0.30-0.91, p = 0.02).

Conclusions: The beneficial effects of PAS on increasing the penile length and glans width were again confirmed. More gain of penile length was expected in the larger penis at baseline. There are no reported increased postoperative complications in association with PAS.

Keywords: Hypospadias; Meta-analysis; Preoperative androgen stimulation; Postoperative complications; Testosterone.

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INTRODUCTION

Hypospadias is a common male genital birth defect wherein the urethral meatus is abnormally displaced ventrally instead of at the tip of the glans [1]. The true worldwide prevalence of hypospadias has not been due to heterogeneity in reported results between countries [2]. The highest mean prevalence of hypospadias was in North America (34.2/10,000 live births), followed by Europe (19.9/10,000 live births). Asian studies reported the prevalence of hypospadias ranged from 0.6 to 69/10000 live births [2].

Many classifications have been suggested, wherein Hadidi's [3] was commonly used. Glanular hypospadias means the meatus is on the glans. The distal hypospadias refers to the meatus which is located from the corona of the glans to the midshaft of the penis, and the proximal hypospadias is about the meatus at the proximal shaft of penis, penoscrotal, scrotal, or perineal areas. While the classification of hypospadias is generally based on the location of the urethral meatus, the meatal location can be changed after the correction of penile curvature [4]. Because the meatal location is one factor that defines hypospadias complexity, some surgeons suggested reclassifying hypospadias after chordee correction to figure out the true severity of hypospadias [3].

The only treatment for hypospadias is surgical repair of the urethral

defect. The aims of hypospadias correction are to make a normal function and normal-looking penis. However, it is a technically demanding procedure with a high complication rate [5-8]. The major complications are urethrocutanous fistula, wound dehiscence, and meatal stenosis [9]. A meta-analysis of complication rates of the tubularized incised plate (TIP) repair showed that the incidence of fistula and meatal stenosis were 5.7% and 3.6% in distal hypospadias and 10.3% and 4.4% in proximal ones [5]. The overall complication rate of proximal hypospadias could be more than 50% [8,10,11]. Several factors could be associated with an increased complication rate, such as proximal hypospadias [12], glans size [13], urethral plate quality [14], and penile curvature [15]. Therefore, preoperative androgen stimulation (PAS) has been applied to increase the glans width [16,17] and promote local vascularity [16,18], which is believed to improve surgical outcomes. Also, PAS increases the penile length, which may improve the cosmetic outcome and parents' satisfaction.

The beneficial effects of PAS on penile biometric changes were revealed in dozens of studies. PAS in hypospadias was first reported in 1982, wherein dihydrotestosterone cream four weeks before the surgery significantly increased both penile length and glans width in about 75% of patients [19]. Since then, PAS has been

used in hypospadias patients and, hypospadias with small penis [20–23], severe hypospadias [21]. Testosterone (intramuscular (IM) [17,20,22], topical [23–25] or oral [21]), human chorionic gonadotropin (IM) [26–28] and dihydrotestosterone (topical) [19,27,29,30] were used with various dosage and duration. PAS increased the penile length by 2.7 mm [20] to 24 mm [31] and glans width by 0.2 mm [32] to 5.3 mm [33]. Although heterogeneity in the reported increase in penile size, there is only a couple of reviews [34,35] that were done on these topics, and no quantitative data have been reported on the amount of the increase in penile length and glans width following PAS. Indeed, PAS can increase the penile size, but how much the penile grows following PAS has not been determined.

Meanwhile, several studies attempted to show that PAS could prevent postoperative complications [21,29,36]. In a randomized controlled trial (RCT) of midshaft or distal hypospadias patients with flat urethral plate who underwent TIP urethroplasty, the treatment group received intramuscular testosterone 2mg/kg once a month for two months, and the control group did not. Results showed that the prevalence of overall complication and fistula in treatment groups were lower than in the controls (5.45% versus 13.18% and 4.39% versus 7.69%, respectively) [36]. Another RCT

included only proximal hypospadias patients, wherein the treatment group received oral testosterone for three months also indicated a lower complication rate in favor of the PAS group [21].

However, several studies demonstrated that PAS could increase [16,37] or had no effect [38] on the complication rate. Results from a RCT of distal hypospadias patients who underwent single-stage urethroplasty showed increased tissue edema at preputial skin and prevalence of wound dehiscence in PAS group compared to the controls. The author also found increased lymphocytic infiltrates and fibrocollagenous tissue of preputial skin in PAS group by hematoxylin and eosin staining, indicating increased inflammation [16]. Concerns about the detrimental effect of PAS on tissue healing were also raised in animal studies. In castrated male rats which underwent the urethroplasty, those who received testosterone showed an increased inflammatory response and prolonged and delayed proliferative phases compared to those who did not [39]. This suggests that PAS may have negative effects on the wound recovery process.

Several meta-analyses attempted to assess the overall postoperative complication rate. In the first two meta-analyses, PAS did not show effects on reducing postoperative complication rate [40,41]. The risk ratio for postoperative complication were

1.67 (95%CI: 0.96–2.91, p = 0.07) [40] and 1.18 (95% CI: 0.70–2.00, p = 0.5) [41]. In the most recent meta-analysis, the pooled analysis of RCTs showed that PAS could significantly decrease the risk of postoperative complication (RR = 0.36, 95%CI: 0.20–0.65, p = 0.0007) [42]. Among the above-mentioned meta-analyses, only one study reported the risk of individual complications such as fistula, wound dehiscence, and stenosis. Thus, whether PAS can reduce the postoperative complication rate is undetermined. Therefore, it is necessary to uncover the role of PAS on postoperative complications in patients with hypospadias.

HYPOTHESIS TESTING

We hypothesized that PAS significantly increases the penile length and glans width. Meanwhile, PAS may not be beneficial to the overall complication rate but to a specific complication. To test our hypothesis, we performed a systematic review of the literature and meta-analysis to address the following questions:

- How much does PAS significantly increase the penile size in patients with hypospadias?
- Are there any variables related to the different increases in penile size following PAS?
- Whether PAS could reduce the risk of overall postoperative complication rate?

- Whether PAS could reduce the risks of major complications such as fistula, wound dehiscence, and stenosis?

METHODS

1. Search strategy

We comprehensively searched the published literature between 1980 and 2022 on Pubmed, Embase, Google Scholar, Scopus, Web of Science, and Proquest. The search terms were hypospadias AND (hormone therapy OR testosterone OR androgen OR dihydrotestosterone OR hormone stimulation OR hormonal stimulation). Filters were time (1980–2022), original article, human, clinical, English, journal article, and male.

2. Eligible criteria

Studies of hypospadias patients aged < 18 who underwent PAS regardless of hormone type or delivery route were included. The results must include at least one of the target variables: changes in penile length, glans width, or postoperative complication rate. Studies of patients with 5-alpha reductase deficiency, disorders of sexual differentiation, or micro-penis without hypospadias were excluded.

3. Screening, assessment, and evaluation of studies

The records were imported to Endnote for title screening, wherein irrelevant studies were removed. To reduce selection bias, the abstract and full-text screening and quality assessment were

done independently by two reviewers. The disagreements on study inclusion were resolved with consensus. Study quality assessment for studies of the changes in penile size was performed using the "NIH quality assessment tool for before-after (Pre-Post) studies with no control group" [37]. Study quality assessment for two-arm trials was done according to the Cochrane collaboration recommendation using the risk of bias assessment tools: ROBINS-I for non-RCT [38] and RoB 2 for RCT [39].

4. Data synthesis

The increase in penile length and glans width following PAS was expressed as a mean difference. The glans was assumed round. Therefore, the glans circumference was reported, and the width was calculated by dividing the circumference by 3.14. When a missing mean or standard deviation exists, data was converted and imputed according to Cochrane's recommendation [40]. The formulas for conversion and imputation were described in detail in the **Appendix.** The risk ratio (RR) was used to assess the complication rate. In this study, postoperative complications were fistula, wound dehiscence, diverticula, and stenosis. Proximal hypospadias included proximal penile, penoscrotal, scrotal, and perineal hypospadias [3].

5. Assessment of heterogeneity and publication bias

Subgroup analysis was used to explore the sources of heterogeneity. Moreover, meta-regression was done to evaluate the effect of pretreatment penile size and proportion of proximal hypospadias on penile growth. Publication bias was assessed using Egger's test.

6. Statistical analysis

Meta-analysis was conducted when appropriate using Stata (version 16.0, StataCorp L.P., College Station, Texas). The random-effects method was used in case of significant heterogeneity between studies (I^2 > 50%). Otherwise, the fixed-effect was used. Meta-regression was done with a single covariate. Statistical significance was set at a $p < 0.05$.

7. Ethics statement

This systematic review and meta-analysis did not involve human subjects or animals, so ethical approval was not required. This study was registered in the international database of prospective systematic reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/). The registration number is CRD42022308539.

RESULTS

1. Search results

The initial literature search yielded 2389 records. A total of 365 duplicated records were excluded automatically. Following an advanced search in reference management software (EndNote), 1856 ineligible records were identified and excluded. Next, 37 duplicated records were found manually and excluded, leaving 131 records for screening. Title and abstract screening led to the exclusion of 84 records, and content screening led to the exclusion of 15 studies. Eventually, 32 studies were eligible for the systematic review and meta-analysis (**Fig. 1**).

2. Characteristics of included studies

A total of 1328 patients were included, with a mean sample size was 37. RCTs accounted for about one-fourth of studies, while case series made up the most. Nine studies did not provide a classification of hypospadias. Small penis and severe hypospadias were mentioned as an indication of PAS, but half of the studies did not state the indication for PAS. Regarding hormones applied in PAS, testosterone was used the most, accounting for about 80% of 39 trials. Dihydrotestosterone, human chorionic gonadotropin, or combined hormone was scantly prescribed. Regarding delivery

route, more than half of the trials were intramuscular (IM). PAS was used with various regimes, wherein testosterone injection once a month for three months or daily application for two or three months was prescribed most frequently (Table 1 and Table 2).

3. Penile length

The increase in penile length was assessed in 21 studies [4,7–9,12,15,22,28–41], wherein 15 [4,7–9,12,22,28–35,38] were available for meta-analysis. All of the included studies used testosterone. Most of the studies had a good or fair quality (Table 3). The missing standard deviation was imputed in six studies (Table 4). The total number of patients was 602.

There was a high between-studies heterogeneity (I^2 = 98.4%). PAS using testosterone increased the penile length significantly by 9.34 mm (95% CI: 6.71–11.97) (Fig. 2). The increase in RCTs was 7.36 mm, whereas it was 10.33 in non-RCTs. However, it was not statistically different (Fig. 3A). Subgroup analysis by delivery route showed that the effect of IM did not differ from topical or oral use (Fig. 3B). The pooled analysis of studies using the same protocol of PAS (IM testosterone, 2 mg/kg, once a month for three months) showed an increase of 10.24 mm (Fig. 4). A longer penis at the baseline was associated with a larger increased length following

PAS (Fig. 5). Penis with 1 mm longer at the baseline was likely to gain a greater increase in penile length by 0.5 mm (coefficient = 0.52, p = 0.006). However, increased penile length was not dependent on the proportion of severe hypospadias in included studies (Table 5). The results of Egger's test revealed no evidence of small-study effect (intercept = 0.92, p = 0.59)

4. Penile glans width

The increase in the glans width following PAS was assessed in 12 studies, wherein all used testosterone [4,5,7,9,22,28,29,31-33,35,42] (Table 4). Most of the studies had a good or fair quality (Table 3). There was a significant between studies' heterogeneity (I2 = 98.07%). PAS with testosterone increased the penile glans width by 3.26 mm (95% CI: 2.50–4.02) (Fig. 6). This increase did not differ between RCTs and non-RCTs (Fig. 7A) or hormone delivery routes (Fig. 7B). Additionally, neither baseline glans size nor the proportion of proximal hypospadias affected the increase in glans width in the meta-regression analysis (Table 5). The results of Egger's test revealed no evidence of small-study effect (intercept = 0.28, p = 0.83)

5. Complication rate

The complication rate was assessed in 18 studies [4,5,8,12-

15,22,29,30,37,43–49], wherein 14 studies, including 5 RCTs [4,5,8,12,13] and 9 non–RSTs [14,15,22,29,43,44,46–48], were available for meta–analysis. All RCTs had some concerns of risk of bias (**Fig. 8A**). More than half of non–RCTs had a serious or critical risk of bias (**Fig. 8B**). The between studies' heterogeneity was significant in the overall complication pool (I2 = 80.95%, **Fig. 9A**) but not significant in the specific complications pool (**Fig. 9B, 9C, and 9D**). Overall, the complication rate was similar between PAS group and the control (RR = 1.08, 95% CI: 0.75–1.54, p = 0.68).

The subgroup analysis by study design observed the different effects of PAS on the complication rate between non–RCTs and RCTs (**Fig. 10A**). However, both groups did not show any statistically significant effect of PAS on the complication rate. Among major postoperative complications (fistula, dehiscence, and stenosis), only the risk of the postoperative fistula was statistically lower in the PAS group than in control (RR = 0.62, 95% CI: 0.41–0.93, p = 0.02) (**Fig. 9B**). The pooled analysis of RCTs indicated that patients with PAS were likely to have two times fewer postoperative fistula than those without PAS. In contrast, non–RCTs showed a neutral effect (**Fig. 10B**). The results of Egger's test revealed no evidence of a small–study effect (intercept = –1.54, p = 0.07).

DISCUSSION

Our study showed that PAS with testosterone significantly increased the penile length and glans width. Moreover, we first found that the increase in penile length is in accordance with baseline length showing the differential response to testosterone. Despite the controversy, PAS was not found to increase the overall complication rate of hypospadias. Instead, the risk of fistula appears to lessen.

Among pediatric urologists, a small-looking penis was the primary indication for the prescription of PAS for hypospadias patients [59,60]. Indeed, PAS significantly increased the penile length by 9 mm. This was again demonstrated in the pooled analysis of the homogenous treatment protocol with intramuscular monthly testosterone for three months resulting in a similar increase in length. This increase in penile size may be of help, allowing to construct a larger bore urethra, reducing some complications such as stricture. However, this benefit may be offset by increased urethral defect to repair that will accompany the penile lengthening. Indeed, it was reported that the length of the urethral defect was independently associated with postoperative fistula [61]. However, considering the average penile length at the baseline in our study was 25.3 mm, which is called to be microphallus or close to the

lower limit of the normal range (–2.5 SD) of boys at this age [62–64], we would expect postoperative penile appearance is likely to be unsatisfactory in terms of protrusion even after complication–free repair. This postoperative concealment of the penis may cause significant cosmetic concern as the children grow. In this regard, the resultant increases in length of up to 1 cm should be taken into account as a significant benefit given the lack of importance of penile growth until entering puberty [63].

Our results also showed a higher hormonal response in the longer penis at baseline. The reason is unknown in the current study, but it might be explained by differential testosterone sensitivity. The smaller penile length at baseline may result from less response to PAS, whereas the larger one showed the reverse. We also attempted to determine whether the difference in posttreatment penile length resulted from a similar hormone response but the difference in penile length at the baseline. The result suggested the penile growth rate is larger in favor of a longer penis at baseline, supporting our claim of higher hormonal response in this group **(Fig. 11)**. This is somewhat disappointing because PAS is actually needed for those with a smaller penis. This could indicate differential doses or schedules may be required to elicit better responses.

Interestingly, no association was found between the proportion of proximal hypospadias and response to PAS. While we easily classified the type based on meatal location, which could be advanced or regressed following completion of the penile degloving. Thus, the classification of distal hypospadias may include those that showed significant retraction of the meatus, which requires division of the urethral plate for the straightening of the penis. This heterogeneity of classification may explain the reason for no difference in hormonal response.

PAS significantly increased the glans width by 3 mm. Even though the extent of penile growth was heterogeneous, our finding of the increase of glans width was in line with the result of a large cohort [65]. They found that the glans width increased by 4 mm following IM testosterone therapy, and two doses led to a significant increase than one dose. Small glans width was a potential risk factor for glandular dehiscence and fistula in hypospadias repair [13], so PAS could improve surgical outcomes.

Although the beneficial effect of PAS on penile growth is undeniable, its effects on reducing postoperative complications remain controversial. Some studies showed that PAS could decrease the complication rate [21,29,36]; others claimed contrasting results [16,27,37]. Animal studies indicated that PAS

could promote inflammation [39] or inhibit wound healing [66]. Several meta-analyses were done [40-42], wherein one [42] showed that the complication rate was in favor of the PAS group than in control. Our results of significantly lower risk of the fistula may be assumed to be consistent with these data because urethrocutaneous fistula consists of the majority of overall complications.

Why PAS could reduce the rate of the fistula is unknown in our study because we cannot control confounders that affect the fistula rate, such as the classification of hypospadias or surgical technique. However, we could suggest some reasons for this beneficial effect of PAS on postoperative complications. First, PAS increased the glans width by about 3 mm, which means the glans circumference increased by about 10 mm. Since glandular closure overlies on urethral closure, elevated tension due to tight glandular closure may inhibit the urinary flow below the glans and predispose the development of a fistula there. Thus, an increased amount of glans for glanuloplasty may be prohibitive from the fistula development by conferring better urinary flow. The increase of glans size by PAS could persist for six months following stimulation [65], so its effect on reducing the wound tension may confer a better chance for fistula-free healing for a prolonged period after surgery. Second,

histological studies showed that PAS could enhance the neovascularization in both the number of vessels and volume density (number of vessels/point) of local tissue [18,20], leading to an increase in the blood supply for the wound healing process. Third, though PAS could promote inflammation [39], which is often presumed to increase wound complication, this is, on the other hand, important for the early hemostasis and the facilitated clearance of bacteria and damaged cells [67] in the acute healing process. However, the effect of inflammation on decreasing the fistula rate is controversial. As a result, PAS could contribute to reducing the fistula rate. To confirm the potential effect of PAS on decreasing the fistula rate, a well-designed RCT may be needed in the future.

We acknowledge the limitations of the current study, which are inherent to meta-analysis and the context of the small number of studies with a small and mixed study population on this topic. First, the meta-analysis of the penile size used 15 single-arm studies, which can lead to an inherent bias due to a lack of a control group. However, we could assume that there is no increase in penile size in patients without PAS, as shown in the control group of RCTs [20,24,36]. Second, the missing standard deviation was imputed in some studies. Although it did not change the effect size, it can affect the weight of these studies in the pooled analysis [67]. Third,

we attempted to perform a meta-regression analysis of penile length and glans width with multiple covariates, which needs ten studies for each covariate [68]. However, we can only control for a single covariate (penile length at baseline or proportion of proximal hypospadias) due to the limited number of studies. Thus, we could not control the effects of other factors on penile growth, such as the dose and duration of PAS. Fourth, even though we found a positive correlation between the penile length at the baseline and the increase in penile length following PAS, it did not necessarily mean a better response rate to testosterone for a longer penis. In other words, while the longer penis may gain more increase than the smaller one but the percentage of increase over the length before treatment may be similar. Indeed, the correlation between the proportion of penile increase and the penile length before treatment was very low (Fig. 12). Thus, we could not claim that the longer penis was more sensitive to PAS than the smaller one. Lastly, the high heterogeneity in the meta-analysis of penile length and glans width may affect the reliability of the pooled analysis [69]. We applied the random effects for meta-analysis, subgroup analysis, and meta-regression to figure out the source of heterogeneity, which may result from the differences in patient selection, such as age, hypospadias grade, PAS protocol, and surgical technique. Our

meta-regression showed that pretreatment penile length is a factor that made the difference in the increase of penile length between studies. Despite the limitations, our efforts to deal with heterogeneity, including subgroup analysis, pooled analysis of homogenous studies, and meta-regression, have contributed to uncovering the effect of PAS on penile size and postoperative complications in patients with hypospadias.

CONCLUSIONS

The beneficial effects of PAS on increasing the penile length and glans width of patients with hypospadias were again confirmed. More gain of penile length was expected in the larger penis at baseline. PAS is not associated with increased postoperative complications.

BIBLIOGRAPHY

1. C. Radmayr (Chair) GB, H.S. Dogan,, J.M. Nijman (Vice-chair) YFHR, M.S. Silay,, R. Stein ST, Guidelines Associates: L.A. 't Hoen JQ, N. Bhatt. EAU Guidelines on Paediatric Urology Edn. presented at the EAU Annual Congress Milan 2021. 2021.
2. Springer A, van den Heijkant M, Baumann S. Worldwide prevalence of hypospadias. J Pediatr Urol 2016;12:152.e1-7.
3. Hadidi AT. Classification of Hypospadias. In: Hadidi AT, Azmy AF, editors. Hypospadias Surgery: An Illustrated Guide. Berlin, Heidelberg: Springer Berlin Heidelberg; 2004. p. 79-82.
4. Sarma VP. The feasibility of urethral plate preservation in proximal and mid-penile hypospadias: sequential and anatomical approach to the repair. Annals of Pediatric Surgery 2020;16:26.
5. Pfistermuller KL, McArdle AJ, Cuckow PM. Meta-analysis of complication rates of the tubularized incised plate (TIP) repair. J Pediatr Urol 2015;11:54-9.
6. Bhat A, Mandal AK. Acute postoperative complications of hypospadias repair. Indian J Urol 2008;24:241-8.
7. Pippi Salle JL, Sayed S, Salle A, Bagli D, Farhat W, Koyle M, et al. Proximal hypospadias: A persistent challenge. Single institution outcome analysis of three surgical techniques over a 10-year period. J Pediatr Urol 2016;12:28.e1-7.
8. Long CJ, Chu DI, Tenney RW, Morris AR, Weiss DA, Shukla AR, et al. Intermediate-Term Followup of Proximal Hypospadias Repair Reveals High Complication Rate. J Urol 2017;197:852-8.
9. Christopher J. Long M, Mark R. Zaontz, MD, and Douglas A. Canning, MD. Hypospadias. In: Alan W. Partin, Roger R. Dmochowski, Louis R. Kavoussi, Craig A. Peters, editors. Campbell-Walsh Urology, 12th ed. Philadelphia, USA: Elsevier; 2021. p. 905-48.
10. McNamara ER, Schaeffer AJ, Logvinenko T, Seager C, Rosoklija I, Nelson CP, et al. Management of Proximal Hypospadias with 2-Stage Repair: 20-Year Experience. J Urol 2015;194:1080-5.
11. Stanasel I, Le HK, Bilgutay A, Roth DR, Gonzales ET, Jr., Janzen N, et al. Complications following Staged Hypospadias Repair Using Transposed Preputial Skin Flaps. J Urol 2015;194:512-6.
12. Eassa W, Jednak R, Capolicchio JP, Brzezinski A, El-Sherbiny M. Risk factors for re-operation following tubularized incised plate urethroplasty: a comprehensive analysis. Urology 2011;77:716-20.
13. Bush NC, Villanueva C, Snodgrass W. Glans size is an independent risk factor for urethroplasty complications after hypospadias repair. J Pediatr Urol 2015;11:355.e1-5.

14. Holland AJ, Smith GH. Effect of the depth and width of the urethral plate on tubularized incised plate urethroplasty. J Urol 2000;164:489-91.
15. Abdelhalim KM, Abdelwahab HA, Abdelgawad E, Kadry AM, Sherief MH. Predictors of successful outcome of tubularized incised plate for primary distal hypospadias repair. African Journal of Urology 2021;27:164.
16. Menon PR, K. L. N. Handu, A. Balan, L. Kakkar, N. Outcome of urethroplasty after parenteral testosterone in children with distal hypospadias. J Pediatr Urol 2017;13:292.e1-.e7.
17. Babu RC, S. The role of preoperative intra muscular testosterone in improving functional and cosmetic outcomes following hypospadias repair: A prospective randomized study. J Pediatr Urol 2018;14:29.e1-.e6.
18. Bastos AN, Oliveira LR, Ferrarez CE, de Figueiredo AA, Favorito LA, Bastos Netto JM. Structural study of prepuce in hypospadias--does topical treatment with testosterone produce alterations in prepuce vascularization? J Urol 2011;185:2474-8.
19. Monfort G, Lucas C. Dehydrotestosterone penile stimulation in hypospadias surgery. Eur Urol 1982;8:201-3.
20. Mohammadipour AH, M. Sharifabad, P. S. Shojaeian, R. Pre-operative hormone stimulation in hypospadias repair: A facilitator or a confounder. J Pediatr Urol 2020;16:318.e1-.e7.
21. Chen C, Gong CX, Zhang WP. Effects of oral testosterone undecanoate treatment for severe hypospadias. Int Urol Nephrol 2015;47:875-80.
22. Khokar DSP, R. V. Can Testosterone Alter the Degree of Hypospadias? A Comprehensive Study. J Indian Assoc Pediatr Surg 2021;26:38-43.
23. Nerli RB, Koura A, Prabha V, Reddy M. Comparison of topical versus parenteral testosterone in children with microphallic hypospadias. Pediatr Surg Int 2009;25:57-9.
24. Paiva KCB, A. N. Miana, L. P. Barros Ede, S. Ramos, P. S. Miranda, L. M. Faria, N. M. Avarese de Figueiredo, A. de Bessa, J., Jr. Netto, J. M. Biometry of the hypospadic penis after hormone therapy (testosterone and estrogen): A randomized, double-blind controlled trial. J Pediatr Urol 2016;12:200.e1-6.
25. Chalapathi G, Rao KL, Chowdhary SK, Narasimhan KL, Samujh R, Mahajan JK. Testosterone therapy in microphallic hypospadias: topical or parenteral? J Pediatr Surg 2003;38:221-3.
26. Koff SA, Jayanthi VR. Preoperative treatment with human chorionic gonadotropin in infancy decreases the severity of proximal hypospadias and chordee. J Urol 1999;162:1435-9.
27. de Mattos e Silva E, Gorduza DB, Catti M, Valmalle AF, Demède D, Hameury F, et al. Outcome of severe hypospadias repair using three different techniques. J Pediatr Urol 2009;5:205-11; discussion 12-4.

28. Gorduza DB, Gay CL, de Mattos ESE, Demède D, Hameury F, Berthiller J, et al. Does androgen stimulation prior to hypospadias surgery increase the rate of healing complications? – A preliminary report. J Pediatr Urol 2011;7:158–61.
29. Kaya C, Bektic J, Radmayr C, Schwentner C, Bartsch G, Oswald J. The efficacy of dihydrotestosterone transdermal gel before primary hypospadias surgery: a prospective, controlled, randomized study. J Urol 2008;179:684–8.
30. Catti M, Lottmann H, Babloyan S, Lortat–Jacob S, Mouriquand P. Original Koyanagi urethroplasty versus modified Hayashi technique: outcome in 57 patients. J Pediatr Urol 2009;5:300–6.
31. Davits RJ, van den Aker ES, Scholtmeijer RJ, de Muinck Keizer–Schrama SM, Nijman RJ. Effect of parenteral testosterone therapy on penile development in boys with hypospadias. Br J Urol 1993;71:593–5.
32. Chukwubuike KE. Single dose of testosterone in children with hypospadias: any effect on the diameter of the glans penis? African Journal of Urology 2021;27:34.
33. Ali MA, Hasanuzzaman M, Palit PK. Efficacy of Preoperative Topical Testosterone Therapy for Micro Phallic Hypospadias: Experience in Dhaka Shishu (Children) Hospital. Dhaka Shishu (Children) Hospital Journal 2018;34:22–5.
34. Netto JM, Ferrarez CE, Schindler Leal AA, Tucci S, Jr., Gomes CA, Barroso U, Jr. Hormone therapy in hypospadias surgery: a systematic review. J Pediatr Urol 2013;9:971–9.
35. Kaya C, Radmayr C. The role of pre–operative androgen stimulation in hypospadias surgery. Transl Androl Urol 2014;3:340–6.
36. Asgari SA, Safarinejad MR, Poorreza F, Asl AS, Ghanaie MM, Shahab E. The effect of parenteral testosterone administration prior to hypospadias surgery: A prospective, randomized and controlled study. J Pediatr Urol 2015;11:143.e1–6.
37. Snodgrass W, Bush N. Re–operative urethroplasty after failed hypospadias repair: how prior surgery impacts risk for additional complications. Journal of pediatric urology 2017;13:289. e1–. e6.
38. Rynja SPdJ, Tpvm Bosch, Jlhr de Kort, L. M. O. Testosterone prior to hypospadias repair: Postoperative complication rates and long–term cosmetic results, penile length and body height. J Pediatr Urol 2018;14:31.e1–.e8.
39. Hofer MD, Cheng EY, Bury MI, Xu W, Hong SJ, Kaplan WE, et al. Androgen Supplementation in Rats Increases the Inflammatory Response and Prolongs Urethral Healing. Urology 2015;85:691–7.
40. Wright I, Cole E, Farrokhyar F, Pemberton J, Lorenzo AJ, Braga LH. Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: a systematic review. J Urol 2013;190:652–59.

41. Chao M, Zhang Y, Liang C. Impact of preoperative hormonal stimulation on postoperative complication rates after hypospadias repair: a meta-analysis. Minerva Urol Nefrol 2017;69:253-61.
42. Chua ME, Gnech M, Ming JM, Silangcruz JM, Sanger S, Lopes RI, et al. Preoperative hormonal stimulation effect on hypospadias repair complications: Meta-analysis of observational versus randomized controlled studies. J Pediatr Urol 2017;13:470-80.
43. National Heart LaBI. National Heart, Lung and Blood Institute (NIH) quality assessment tool for before-after (Pre-Post) study without control group [Internet]. National Heart, Lung and Blood Institute Homepage. Available from: Available online: http://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed on 26 April 2022).
44. Sterne JAC HM, McAleenan A, Reeves BC, Higgins JPT. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022): Cochrane; 2022. p. Available from www.training.cochrane.org/handbook.
45. Higgins JPT SJ, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022): Cochrane; 2022. p. Available from www.training.cochrane.org/handbook.
46. Higgins JPT, Li T, JJ D. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022): Cochrane; 2022. p. Available from www.training.cochrane.org/handbook.
47. Abdallah B. Topical Testosterone Therapy Prior to Hypospadias Repair (Our experience at Queen Rania Al-Abdullah Hospital for Children). Sch J App Med Sci 2021;5:710-3.
48. Wali IM, AbouZeid AA, Radwan NA, GadAllah MAS, Ghanem WA, El-Naggar O. Preoperative topical testosterone for penile hypospadias repair a comparative study . Annals of Pediatric Surgery 2020;16:38.
49. Chaubey D, Rahul SK, Hasan Z, Thakur VK, Kumar V, Prasad R, et al. Role of Pre-Surgery Testosterone on Phallic Size in Hypospadias Patients. Journal of Indira Gandhi Institute Of Medical Sciences 2020;6:122.
50. Ali MA, Palit PK, Hasanuzzaman M. Efficacy of Preoperative Intramuscular Testosterone Therapy for Micro-phallic Hypospadias. BANGLADESH J CHILD HEALTH 2019;343:85-9.
51. Ahmad R, Chana RS, Ali SM, Khan S. Role of parenteral testosterone in hypospadias: A study from a teaching hospital in India. Urology annals 2011;3:138.

52. Luo CC, Lin JN, Chiu CH, Lo FS. Use of parenteral testosterone prior to hypospadias surgery. Pediatr Surg Int 2003;19:82-4.
53. Sakakibara N, Nonomura K, Koyanagi T, Imanaka K. Use of testosterone ointment before hypospadias repair. Urol Int 1991;47:40-3.
54. Gearhart JP, Jeffs RD. The use of parenteral testosterone therapy in genital reconstructive surgery. J Urol 1987;138:1077-8.
55. Snodgrass W, Bush N. Tubularized incised plate proximal hypospadias repair: Continued evolution and extended applications. J Pediatr Urol 2011;7:2-9.
56. McNamara ER, Schaeffer AJ, Logvinenko T, Seager C, Rosoklija I, Nelson CP, et al. Management of proximal hypospadias with 2-stage repair: 20-year experience. The Journal of urology 2015;194:1080-5.
57. Snodgrass W, Cost N, Nakonezny PA, Bush N. Analysis of risk factors for glans dehiscence after tubularized incised plate hypospadias repair. The Journal of urology 2011;185:1845-51.
58. Rigamonti W, Castagnetti M. Onlay on albuginea: modified onlay preputial island flap urethroplasty for single-stage repair of primary severe hypospadias requiring urethral plate division. Urology 2011;77:1498-502.
59. Malik RD, Liu DB. Survey of pediatric urologists on the preoperative use of testosterone in the surgical correction of hypospadias. J Pediatr Urol 2014;10:840-3.
60. Ezomike UO, Nwangwu EI, Chukwu IS, Ekenze SO. Practice patterns of preoperative hormonal stimulation in pediatric penile surgeries-A survey of Nigerian pediatric surgeons. J Pediatr Urol 2020;16:440-5.
61. Sheng X, Xu D, Wu Y, Yu Y, Chen J, Qi J. The risk factors of Urethrocutaneous fistula after hypospadias surgery in the youth population. BMC Urology 2018;18:64.
62. Park SK, Ergashev K, Chung JM, Lee SD. Penile circumference and stretched penile length in prepubertal children: A retrospective, single-center pilot study. Investig Clin Urol 2021;62:324-30.
63. Boas M, Boisen KA, Virtanen HE, Kaleva M, Suomi AM, Schmidt IM, et al. Postnatal penile length and growth rate correlate to serum testosterone levels: a longitudinal study of 1962 normal boys. Eur J Endocrinol 2006;154:125-9.
64. Cheng PK, Chanoine JP. Should the definition of micropenis vary according to ethnicity? Horm Res 2001;55:278-81.
65. Mittal S, Eftekharzadeh S, Christianson SS, Hyacinthe N, Tan C, Weiss DA, et al. Quantifying Glans Width Changes in Response to Preoperative Androgen Stimulation in Patients Undergoing Hypospadias Repair. J Urol 2022 Feb 11 [Epub] DOI:10.1097/ju.0000000000002481.101097ju0000000000002481.
66. Ashcroft GS, Mills SJ. Androgen receptor-mediated inhibition of cutaneous wound healing. J Clin Invest 2002;110:615-24.

67. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin Wound Healing: An Update on the Current Knowledge and Concepts. Eur Surg Res 2017;58:81-94.
68. Idris NRN, Robertson C. The Effects of Imputing the Missing Standard Deviations on the Standard Error of Meta Analysis Estimates. Communications in Statistics - Simulation and Computation 2009;38:513-26.
69. Deeks JJ HJ, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022): Cochrane; 2022. p. Available from www.training.cochrane.org/handbook.
70. Melsen WG, Bootsma MCJ, Rovers MM, Bonten MJM. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clinical Microbiology and Infection 2014;20:123-9.

Table 1. Summary of included studies

Author/ Year/ Country	Study design	N	Mean age±SD (Range)	Classification of hypospadias	Indication	Hormone used	Delivery route	Dosage	Number of dose/Time of use
Chukwubuike et al., 2021 (Nigeria) [32]	RCT	32	3.1 (1–7)	Coronal: 19 Distal penile: 6 Mid penile: 4 Proximal: 3	NS	T	IM	2mg/kg	1 dose
Khokar et al., 2021 (India) [22]	Prospective case series	45	NS	Anterior: 0 Midshaft: 14 Proximal: 31	Small penis	T	IM	2mg/kg	NS
Abdallah et al., 2021 (Jordan) [47]	Case-control	84	0.5–6	Glandular: 6 Coronal: 33 Distal shaft: 34 Midshaft: 11	NS	T	Top	1x/day	21 days
Mohammadipour et al., 2020 (Iran) [20]	Non-RCT	18	13.6±4.3 mos	Distal penile:14 Other: 4	Small penis	T	IM	25 mg 1x/mo	3 mos
Wali et al., 2020 (Egypt) [48]	Non-RCT	20	18(6–36) mos	NS	Glans diameter < 14 mm	T	Top	NS	30 days
Chaubey et al., 2020 (India) [49]	Prospective case series	17	3.75(2.5–5.5)	Distal penile: 9 Mid penile:2 Proximal penile: 2 Penoscrotal: 3 Perineal: 1	NS	T	IM	2mg/kg 1x/mo	3 mos
Ali et al., 2019 (Bangladesh) [50]	Prospective case series	70	34.86±15.04 (6–60) mos	NS	Small penis	T	IM	2mg/kg 1x/mo	3 mos

Babu et al., 2018 (India) [17]	RCT	94	13.5±1 (12–15) mos	Distal penile: 94	NS	T	IM	2mg/kg 1x/mo	3 mos
Rynja et al., 2018 (Netherlands) [38]	Case-control	24	1.2±0.5	Anterior: 12 Midshaft: 3 Proximal penile: 9	NS	T	NS	NS	NS
Ali et al., 2018 (Bangladesh) [33]	Retrospective case series	35	33.51±19.9 mos	Anterior: 6 Middle: 23 Posterior: 6	Small penis	T	Top	3x/day	3 ws
Snodgrass et al., 2017 (USA) [37]	Cohort	139	3.4±6.8	NS	Glans with < 14mm	T	NS	NS	NS
Menon et al., 2017 (India) [16]	RCT	49	3(1–12)	Anterior: 49	Without small penis	T	IM	2mg/kg 1x/mo	3 mos
Paiva et al., 2016 (Brazil) [24]	RCT	28	31.39 ± 25.96 mos	Anterior: 16 Midshaft: 5 Proximal penile: 7	NS	T	Top	2x/day	30 days
McNamara et al., 2015 (USA) [10]	Retrospective case series	66	8.9±4.0	NS	NS	T	NS	NS	NS
Asgari et al., 2015 (Iran) [36]	RCT	91	32.1±6.2 mos	Anterior: 65 Midshaft: 26	NS	T	IM	2mg/kg 1x/mo	2 mos

Chen et al., 2015 (China) [21]	RCT	34	21.6±14.3 mos	Proximal penile: 10 Penoscrotal: 15 Perineal: 9	Microphallic hypospadias/ Severe hypospadias	T	PO	2mg/kg 1x/day	3 mos
Gorduza et al., 2011 (France) [28]	Case-control	30	41 (10–97) mos	Severe: 5	Small penis	HCG	IM	1500IU x 1x/2 days	12 days
				Severe: 9		T	IM	100mg/m^2 1x/mo	2–6 doses/ 2–6 mos
				Severe: 16		HCG and T	IM	NS	NS
Snodgrass et al., 2011 (USA) a [56]	Cohort	32	19.4±33.3 (3–420) mos	NS	Small looking glans	T	IM	2mg/kg 1x/3 ws	2–3 doses/ 6–9 ws
Snodgrass et al., 2011 (USA) b [55]	Cohort	8	18(3–117) mos	NS	Small looking glans	T	IM	2mg/kg 1x/3–4 ws	3 doses/ 9–12 ws
Rigamonti et al., 2011 (Italy) [57]	Case series	9	16(10–30) mos	NS	NS	T	IM	1x/mo	2–3 doses/ 2–3 mos
Ahmad et al., 2011 (India) [51]	Prospective case series	23	4.6(0.5–10)	Gladunar: 3 Subcoronal: 2 Distal penile: 4 Midshaft: 5 Proximal penile: 9	NS	T	IM	2mg/kg 1x/w	3 ws

Nerli et al., 2009 (India) [23]	RCT	10	19(16–27) mos	Penile: 10 Penoscrotal: 8 Perineal: 3	Small penis	T	IM	2mg/kg 1x/m	3 mos
		11				T	Top	2mg/kg 1x/day	21 days
de Mattos e Silva et al., 2009 (France) [27]	Retrospective case series	73	24(1–105) mos	NS	Small penis	HCG	IM	1500IU x 1x/2 days	12 days
						T	IM	100mg/m^2	NS
						DHT	Top	x1/day	60 days
Catti et al., 2009 (France) [30]	Case series	26	23(9–40) mos	Proximal penile: 26	Small glans/ Glans with < 14mm	T	IM	100mg/m^2	NS
						DHT	Top	NS	NS
Kaya et al., 2008 (Autria) [29]	RCT	37	30.8±5.4 (11.3–152.1) mos	Coronal: 26 Penile: 9 Penoscrotal:2	NS	DHT	Top	2.5% 1x/day	3 mos
Luo et al, 2003 (Taiwan) [52]	Case series	25	6–18 mos	Penile: 8 Penoscrotal: 15 Perineal: 2	Small penis	T	IM	25 mg 1x/mo	3 mos

Chalapathi et al., 2003 (India) [25]	Non-RCT	13	1–10	Coronal: 4 Distal penile: 4 Mid penile: 3 Proximal penile: 6 Penoscrotal: 9	Small penis	T	Top	2x /day	21 days
		13				T	IM	2mg/kg 1x/w	3 ws
Koff et al., 1999 (USA) [26]	Case series	12	6–12 mos	Proximal penile: 12	NS	HCG	IM	250 IU or 500 IU 2x/w	5 ws
Davits et al., 1993 (Netherlands) [31]	Case series	40	27.3±13.74 mos	NS	NS	T	IM	2mg/kg x2 (2nd and 5th week pre–operative)	5 ws
Sakakibara et al., 1991 (Japan) [53]	Case series	15	4.1(2.9–9.5)	Penile: 4 Penoscrotal: 6 Scrotal: 4 Perineal: 1	NS	T	Top	0.2–0.4 g 1x/day x 3w (1 cycle)	1–10 cycles/ 3–30 ws
Gearhart et al., 1987 (USA) [54]	Case series	36	2.3	Coronal: 4 Distal penile: 7 Midshaft: 16 Penoscrotal: 3 Redo: 6	NS	T	IM	2mg/kg x2 (2nd and 5th week pre–operative)	5 ws
Monfort et al., 1982 (France) [19]	Case series	45	0–16	Anterior: 5 Penile: 13 Posterior: 27	NS	DHT	Top	0.6–1g/day according age	4 ws

RCT: Randomized controlled trial; Non-RCT: Non-randomized interventional studies; SD: Standard Deviation; PO: Oral; IM: intramuscular; Top: Topical; NS: Not specified; mo(s): month(s); w(s): week(s); T: Testosterone; HCG: Human chorionic gonadotropin; DHT: Dihydrotestosterone; IU: International Unit; Mean age and its standard deviation is expressed in years otherwise specified.

Table 2. Characteristics of included studies

Parameters	N	%
Range of age (N = 32)	0.5–16	
Mean sample size ± SD (Range) (N = 32)	36.7 ± 29.2 (8–139)	
Country (N = 32)		
North America (United States)	6	18.8
South America (Brazil)	1	3.1
Middle Eastern (Egypt, Iran, Jordan)	4	12.5
Asia (China, Bangladesh, India, Japan, Taiwan)	12	37.5
Africa (Nigeria)	1	3.1
Europe (Austria, France, Italy, Netherlands)	8	25.0
Study design (N = 32)		
Randomized controlled trial	8	25.0
Non-randomized controlled trial	3	9.4
Cohort	3	9.4
Case-control	3	9.4
Case series	15	46.8
Indications (N = 32)		
Small penis	15	46.8
Small penis / Severe hypospadias	1	3.2
Not specified	16	50.0
Classification of hypospadias (N = 32)		
Yes	23	71.9
No	9	28.1
Types of Hormones used in trials (N = 39)		
Testosterone	31	79.5
Dihydrotestosterone	4	10.2
Human chorionic gonadotropin	3	7.7
Human chorionic gonadotropin and Testosterone	1	2.6
Hormone delivery route in trials (N = 39)		
Intramuscular	24	61.5
Topical	11	28.2
Oral	1	2.6
Not specified	3	7.7
Intramuscular testosterone (N =20)		
Single dose (2mg/kg)	1	5
Two doses (2mg/kg twice in 5ws(2), 2mg/kg 1x/mo(1))	3	15
Three doses (2mg/kg 1x/mo (6) or 2mg/kg 1x/w (2) or 25 mg 1x/mo (2))	10	50
Other	6	30
Number of studies by outcomes (N = 32)		
Increase of penile length	20	62.5
Increase of glans width	12	37.5
Postoperative complication rate	17	53.1

SD: Standard Deviation; mo(s): month(s); w(s): week(s)

Table 3. Quality assessment for the included studies evaluating the increase of the penile size following preoperative hormone stimulation

Author, year (country)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Overall**
Khokar et al., 2021 (India)	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Good**
Abdallah et al., 2021 (Jordan)	**N**	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**N**	**Y**	**N**	**N**	**N**	**Poor**
Chukwubuike et al., 2021 (Nigeria)	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**N**	**Good**
Mohammadipour et al., 2020 (Iran)	**Y**	**Y**	**N**	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Good**
Wali et al., 2020 (Egypt)	**Y**	**N**	**N**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Fair**
Chaubey et al., 2020 (India)	**Y**	**N**	**CD**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Fair**

Ali et al., 2019 (Bangladesh)	**Y**	**N**	**Y**	**CD**	**Y**	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Fair**
Ali et al., 2018 (Bangladesh)	**Y**	**N**	**Y**	**CD**	**N**	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Fair**
Babu et al., 2018 (India)	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**N**	**Good**
Menon et al., 2017 (India)	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**N**	**Good**
Paiva et al., 2016 (Brazil)	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Good**
Chen et al., 2015 (China)	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**N**	**Good**
Asgari et al., 2015 (Iran)	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**Good**
Ahmad et al., 2011 (India)	**Y**	**N**	**Y**	**CD**	**N**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Fair**

Nerli et al., 2009 (India)	**Y**	**N**	**N**	**CD**	**N**	**Y**	**N**	**N**	**Y**	**Y**	**N**	**Y**	**Poor**
Luo et al., 2003 (Taiwan)	**N**	**N**	**N**	**CD**	**N**	**Y**	**N**	**N**	**Y**	**Y**	**N**	**Y**	**Poor**
Davits et al., 1993 (Netherlands)	**Y**	**N**	**NS**	**CD**	**Y**	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**N**	**Fair**

Q: Question; NS: Not specified; T: Testosterone; Y: Yes; N: No; CD: cannot determine; NA: not applicable; NR, not reported

NIH quality assessment tool for before-after (Pre-Post) study without control group[1]

1. Was the study question or objective clearly stated?
2. Were eligibility/selection criteria for the study population prespecified and clearly described?
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
4. Were all eligible participants that met the prespecified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the test/service/intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?

8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

1. National Heart, Lung and Blood Institute (NIH) quality assessment tool for before-after (Pre-Post) study without control group [Available online: http://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed on 26 April 2022).]

Table 4. Changes in penile length and glans width following preoperative testosterone stimulation

Author, year (country)	N	Mean age±SD (Range)	Delivery route, Duration of hormone used	Penile length			Penile glans width		
				Baseline (mm) (mean ± SD)	After PAS (mean ± SD)	Mean change ± SD	Baseline (mm) (mean ± SD)	After PAS (mean ± SD)	Mean change ± SD
Chukwubuike et al., 2021 (Nigeria) [32]	32	3.1 (1–7)	IM, single dose	NS	NS	NS	17.6±2.5	17.8±2.3	0.2±2.41#
Khokar et al., 2021 (India) [22]	45	NS	IM, NS	16.87±3.96	26.07±6.99	9.2±4.1	6.84±1.15	9.91±2.77	3.07±3.03
Abdallah et al., 2021 (Jordan) [47]	84	0.5–6	Top, 21 days	31	42.2	11.2±4	12.1	17.2	5.1±1.8
Mohammadipour et al., 2020 (Iran) [20]	18	13.6±4.3 mos	IM, 3 mos	28.9±4.19	31.6±3.77	2.7±4#	12.8±1.04	16.8±1.27	4±1.17#

Wali et al., 2020 (Egypt) [48]	20	18(6–36) mos	Top, 30 days	15.1±2.8	19.9±4.6	4.8±3.8	10.45±1.64	13.55±1.1	3.1±1.45
Chaubey et al., 2020 (India) [49]	17	3.75(2.5–5.5)	IM, 3 mos	27.8±2.98	41.3±2.72	13.5±1.17	NS	NS	NS
Ali et al., 2019 (Bangladesh) [50]	70	34.86±15.04 (6–60) mos	IM, 3 mos	26.1±5.7	39.3±3.9	13.2±26.7#	10.9±1.8	16.2(1.1)	5.3±10.74#
Babu et al., 2018 (India) [17]	94	13.5±1 (12–15) mos	IM, 3 mos	NS	NS	NS	12.85±1.6	14.9±1.8	2.05±5.8#
Ali et al., 2018 (Bangladesh) [33]	35	33.51±19.9 mos	Top, 3ws	27.1±5	34.6±2.6	7.5±12.32#	11.3±1.8	15.2±0.9	3.9±5.24#
Menon et al., 2017 (India) [16]	49	3(1–12)	IM, 3 mos	35.88±6.72	46.85±7.94	10.97±21.91#	15±2.7	20±0.3	5±2.9#
Paiva et al., 2016 (T) (Brazil) [24]	28	31.39 ± 25.96 mos	Top, 30 days	NS	NS	8±9	NS	NS	1.7±3.1
Asgari et al., 2015	91	32.1±6.2 mos	IM, 2 mos	28.3±2.2	38.5±2.6	10.2±2.42#	NS	NS	NS

(Iran) [36]									
Chen et al., 2015 (China) [21]	34	21.6±14.3 mos	PO, 3 mos	19.3±4.4	22.9±5.3	10.6±5.3	NS	NS	NS
Ahmad et al., 2011 (India) [51]	23	4.6(0.5–10)	IM, 3 ws	30.1±13.9	43.6±13.8	13.5±4	NS	NS	NS
Nerli et al., 2009 (IM) (India) [23]	10	19(16–27) mos	IM, 3 mos	20.4±1.5	24.16±1.4	3.76±4.3*	8.75±0.09	12.00±0.09	3.25±0.44#
Nerli et al., 2009 (Top) (India) [23]	11	19(16–27) mos	Top, 3ws	20.58±1.5	24.34±1.2	3.76±3.5*	8.86±0.009	12.04±0.006	3.18±0.09#
Luo et al., 2003 (Taiwan) [52]	25	6–18 mos	IM, 3 mos	19.8±2.4	23.8±2	4.0±5.34*	8.73±0.45	11.91±0.64	3.18±0.6#
Davits et al., 1993 (Netherlands) [31]	40	27.3±13.74 mos	IM, 5 ws	35±11	59±11	24±11#	NS	NS	NS

PAS: preoperative androgen stimulation; PO: Oral; IM: intramuscular; Top: Topical; NS: Not specified; mo(s): month(s); w(s): week(s); SD: Standard Deviation; NS: Not specified; #: imputation; *: conversion; Mean age and its standard deviation is expressed in years otherwise specified.

Table 5. Meta-regression analysis for the increase of penile length and glans width

Covariate	N	Coefficient	SE	z	p-value	95 % CI
Penile length						
Penile lenght at baseline	15	0.52	0.19	2.73	0.006	−0.15 - 0.90
Proportion of proximal hypospadias	10	−1.83	3.02	−0.61	0.54	7.74 - 13.63
Glans width						
Glans width at baseline	12	−0.10	0.13	−0.74	0.46	−0.37 - −0.17
Proportion of proximal hypospadias	8	−0.18	2.50	−0.07	0.94	1.33 - 5.05

N: number of studies; SE: Standard error of the mean; CI: confidence interval

Table 6. Postoperative overall complication rate

Author/ Year/ Country	Study design	Mean age±SD (Range)	Classification of hypospadias of treatment group	Classification of hypospadias of control	Hormone used/ Route/ Dose	Surgical technique	PAS group (No. of pts with complication/ without complication)	Control group (No. of pts with complication/ without complication)
Kaya et al., 2008 (Autria) [22]	RCT	30.8±5.4 (11.3–152.1) mos	Coronal: 26 Penile: 9 Penoscrotal:2	Coronal: 32 Penile: 6 Penoscrotal: 0	DHT/ Top 2.5% 1x/day 3 mos	TIP	1/36	7/31
de Mattos e Silva et al., 2009 (France) [20]	Non-RCT	24(1–105) mos	Severe hypospadias	Severe hypospadias	HCG/IM T/IM DHT/Topical	Buccal muscosa graft, Koyanagi	38/35	30/81
Gorduza et al., 2011 (France) [21]	Non-RCT	41 (10–97) mos	Severe hypospadias	Severe hypospadias	HCG/IM T/IM HCG/IM and T/IM	Onlay, Buccal graft, Koyanagi	9/27	17/79
Snodgrass et al., 2011 (USA) a [51]	Non-RCT	19.4±33.3 (3–420) mos	NS	NS	T/IM 2mg/kg 1x/3 w 2-3 doses	TIP	4/28	30/582
Snodgrass et al., 2011 (USA) b [49]	Non-RCT	18(3–117) mos	NS	NS	T/IM 2mg/kg 1x/3 w 3-4 doses	TIP	1/7	2/14
Asgari et al., 2015 (Iran) [29]	RCT	32.1±6.2 mos	Anterior: 65 Midshaft: 26	Anterior: 61 Midshaft: 30	T/IM 2mg/kg 1x/mo 2 doses	TIP	5/86	12/79
Chen et al., 2015 (China) [14]	RCT	21.6±14.3 mos	Proximal penile: 10 Penoscrotal: 15 Perineal: 9	Proximal penile: 10 Penoscrotal: 19 Perineal: 7	T/IM 2mg/kg 1x/day 90 doses	Duckett technique Or combination	5/29	15/21

						of Duckett and Thiersch–Duplay techniques		
McNamara et al., 2015 (USA) [50]	Non-RCT	8.9±4.0	Proximal	Proximal	T	Retik 2-stage proximal hypospadias repair	33/33	38/30
Menon et al., 2017 (India) [9]	RCT	3(1–12)	Anterior: 49	Anterior: 45	T/IM 2mg/kg 1x/mo 3 doses	Snodgrass, Mathieu, Thiersch Duplay, Onlay technique	12/37	7/38
Snodgrass et al., 2017 (USA) [30]	Non-RCT	3.4±6.8	NS	NS	T	TIP Inlay Two-stage graft	36/59	130/914
Babu et al., 2018 (India) [10]	RCT	13.5±1 (12–15) mos	Distal penile: 94	Distal penile: 92	T/IM 2mg/kg 1x/mo 3 doses	TIP	22/72	26/66
Rynja et al., 2018 (Netherlands) [31]	Non-RCT	1.2±0.5	Anterior: 12 Midshaft: 3 Proximal penile: 9	Anterior: 31 Midshaft: 3 Proximal penile: 2	T/ IM or Top	Mathieu, meatal advancement and glanuloplasty (MAGPI) Technique for distal hypospadias; vascularised preputial tube or onlay island flap Technique for	19/5	23/13

						proximal hypospadias		
Wali et al., 2020 (Egypt) [42]	Non-RCT	18(6–36) mos	NS	NS	T Top 30 days	TIP Two-stage	8/12	8/12
Abdallah et al., 2021 (Jordan) [41]	Non-RCT	0.5–6	Glandular: 6 Coronal: 33 Distal shaft: 34 Midshaft: 11	Glandular: 26 Coronal: 39 Distal shaft: 20 Midshaft: 13	T Top 21 days	NS	14/70	26/72

RCT: Randomized controlled trial; Non-RCT: Non-randomized interventional studies; SD: Standard Deviation; PO: Oral; IM: intramuscular; Top: Topical; NS: Not specified; mo(s): month(s); w(s): week(s); T: Testosterone; HCG: Human chorionic gonadotropin; DHT: Dihydrotestosterone; TIP: Tubularized incised plate; pts: patients; Mean age and its standard deviation is expressed in years otherwise specified.

Table 7. Postoperative fistula rate

Author/ Year/ Country	Study design	Mean age±SD (Range)	Classification of hypospadias of treatment group	Classification of hypospadias of control	Hormone used/ Route/ Dose	Surgical technique	PAS group (No. of pts with complication/ without complication)	Control group (No. of pts with complication/ without complication)
Kaya et al., 2008 (Autria) [22]	RCT	30.8±5.4 (11.3–152.1) mos	Coronal: 26 Penile: 9 Penoscrotal:2	Coronal: 32 Penile: 6 Penoscrotal: 0	DHT Top 2.5% 1x/day 3 mos	TIP	1/36	4/34
Asgari et al., 2015 (Iran) [29]	RCT	32.1±6.2 mos	Anterior: 65 Midshaft: 26	Anterior: 61 Midshaft: 30	T/IM 2mg/kg 1x/mo 2 doses	TIP	4/87	7/84
Chen et al., 2015 (China) [14]	RCT	21.6±14.3 mos	Proximal penile: 10 Penoscrotal: 15 Perineal: 9	Proximal penile: 10 Penoscrotal: 19 Perineal: 7	T/IM 2mg/kg 1x/day 90 doses	Duckett technique Or combination of Duckett and Thiersch–Duplay techniques	2/32	9/27
Menon et al., 2017 (India) [9]	RCT	3(1–12)	Anterior: 49	Anterior: 45	T/IM 2mg/kg 1x/mo 3 doses	Snodgrass, Mathieu, Thiersch Duplay, Onlay technique	5/44	7/38
Babu et al., 2018 (India) [10]	RCT	13.5±1 (12–15) mos	Distal penile: 94	Distal penile: 92	T/IM 2mg/kg 1x/mo 3 doses	TIP	6/88	7/85

Rynja et al., 2018 (Netherlands) [31]	Non-RCT	1.2±0.5	Anterior: 12 Midshaft: 3 Proximal penile: 9	Anterior: 31 Midshaft: 3 Proximal penile: 2	T/ IM or Top	Mathieu, meatal advancement and glanuloplasty (MAGPI) Technique for distal hypospadias; vascularised preputial tube or onlay island flap Technique for proximal hypospadias	6/18	10/26
Wali et al., 2020 (Egypt) [42]	Non-RCT	18(6–36) mos	NS	NS	T Top 30 days	TIP Two-stage	4/16	5/15
Abdallah et al., 2021 (Jordan) [41]	Non-RCT	0.5–6	Glandular: 6 Coronal: 33 Distal shaft: 34 Midshaft: 11	Glandular: 26 Coronal: 39 Distal shaft: 20 Midshaft: 13	T Top 21 days	NS	4/80	7/91

RCT: Randomized controlled trial; Non-RCT: Non-randomized interventional studies; SD: Standard Deviation; PO: Oral; IM: intramuscular; Top: Topical; NS: Not specified; mo(s): month(s); w(s): week(s); T: Testosterone; HCG: Human chorionic gonadotropin; DHT: Dihydrotestosterone; TIP: Tubularized incised plate; pts: patients; Mean age and its standard deviation is expressed in years otherwise specified.

Table 8. Postoperative dehiscence rate

Author/ Year/ Country	Study design	Mean age±SD (Range)	Classification of hypospadias of treatment group	Classification of hypospadias of control	Hormone used/ Route/ Dose	Surgical technique	PAS group (No. of pts with complication/ without complication)	Control group (No. of pts with complication/ without complication)
Kaya et al., 2008 (Autria) [22]	RCT	30.8±5.4 (11.3–152.1) mos	Coronal: 26 Penile: 9 Penoscrotal:2	Coronal: 32 Penile: 6 Penoscrotal: 0	DHT Top 2.5% 1x/day 3 mos	TIP	0/37	3/35
Snodgrass et al., 2011 (USA) a [51]	Non-RCT	19.4±33.3 (3–420) mos	NS	NS	T/IM 2mg/kg 1x/3 w 2-3 doses	TIP	4/28	30/582
Asgari et al., 2015 (Iran) [29]	RCT	32.1±6.2 mos	Anterior: 65 Midshaft: 26	Anterior: 61 Midshaft: 30	T/IM 2mg/kg 1x/mo 2 doses	TIP	0/91	1/90
Chen et al., 2015 (China) [14]	RCT	21.6±14.3 mos	Proximal penile: 10 Penoscrotal: 15 Perineal: 9	Proximal penile: 10 Penoscrotal: 19 Perineal: 7	T/IM 2mg/kg 1x/day 90 doses	Duckett technique Or combination of Duckett and Thiersch–Duplay techniques	0/34	0/36
Menon et al., 2017 (India) [9]	RCT	3(1–12)	Anterior: 49	Anterior: 45	T/IM 2mg/kg 1x/mo 3 doses	Snodgrass, Mathieu, Thiersch Duplay, Onlay technique	7/42	0/45

Babu et al., 2018 (India) [10]	RCT	13.5±1 (12–15) mos	Distal penile: 94	Distal penile: 92	T/IM 2mg/kg 1x/mo 3 doses	TIP	7/87	13/79
Rynja et al., 2018 (Netherlands) [31]	Non-RCT	1.2±0.5	Anterior: 12 Midshaft: 3 Proximal penile: 9	Anterior: 31 Midshaft: 3 Proximal penile: 2	T/ IM or Top	Mathieu, meatal advancement and glanuloplasty (MAGPI) Technique for distal hypospadias; vascularised preputial tube or onlay island flap Technique for proximal hypospadias	2/22	4/32
Wali et al., 2020 (Egypt) [42]	Non-RCT	18(6–36) mos	NS	NS	T Top 30 days	TIP Two-stage	1/19	1/19
Abdallah et al., 2021 (Jordan) [41]	Non-RCT	0.5–6	Glandular: 6 Coronal: 33 Distal shaft: 34 Midshaft: 11	Glandular: 26 Coronal: 39 Distal shaft: 20 Midshaft: 13	T Top 21 days	NS	3/81	14/84

RCT: Randomized controlled trial; Non-RCT: Non-randomized interventional studies; SD: Standard Deviation; PO: Oral; IM: intramuscular; Top: Topical; NS: Not specified; mo(s): month(s); w(s): week(s); T: Testosterone; HCG: Human chorionic gonadotropin; DHT: Dihydrotestosterone; TIP: Tubularized incised plate; pts: patients; Mean age and its standard deviation is expressed in years otherwise specified.

Table 9. Postoperative stenosis rate

Author/ Year/ Country	Study design	Mean age±SD (Range)	Classification of hypospadias of treatment group	Classification of hypospadias of control	Hormone used/ Route/ Dose	Surgical technique	PAS group (No. of pts with complication/ without complication)	Control group (No. of pts with complication/ without complication)
Kaya et al., 2008 (Autria) [22]	RCT	30.8±5.4 (11.3–152.1) mos	Coronal: 26 Penile: 9 Penoscrotal:2	Coronal: 32 Penile: 6 Penoscrotal: 0	DHT Top 2.5% 1x/day 3 mos	TIP	0/37	2/36
Asgari et al., 2015 (Iran) [29]	RCT	32.1±6.2 mos	Anterior: 65 Midshaft: 26	Anterior: 61 Midshaft: 30	T/IM 2mg/kg 1x/mo 2 doses	TIP	1/90	1/90
Chen et al., 2015 (China) [14]	RCT	21.6±14.3 mos	Proximal penile: 10 Penoscrotal: 15 Perineal: 9	Proximal penile: 10 Penoscrotal: 19 Perineal: 7	T/IM 2mg/kg 1x/day 90 doses	Duckett technique Or combination of Duckett and Thiersch–Duplay techniques	0/34	3/33
Babu et al., 2018 (India) [10]	RCT	13.5±1 (12–15) mos	Distal penile: 94	Distal penile: 92	T/IM 2mg/kg 1x/mo 3 doses	TIP	9/85	6/86
Rynja et al., 2018 (Netherlands) [31]	Non-RCT	1.2±0.5	Anterior: 12 Midshaft: 3 Proximal penile: 9	Anterior: 31 Midshaft: 3 Proximal penile: 2	T/ IM or Top	Mathieu, meatal advancement and glanuloplasty (MAGPI) Technique for	7/17	7/29

						distal hypospadias; vascularised preputial tube or onlay island flap Technique for proximal hypospadias		
Wali et al., 2020 (Egypt) [42]	Non-RCT	18(6–36) mos	NS	NS	T Top 30 days	TIP Two-stage	3/17	2/18
Abdallah et al., 2021 (Jordan) [41]	Non-RCT	0.5–6	Glandular: 6 Coronal: 33 Distal shaft: 34 Midshaft: 11	Glandular: 26 Coronal: 39 Distal shaft: 20 Midshaft: 13	T Top 21 days	NS	7/77	6/92

RCT: Randomized controlled trial; Non-RCT: Non-randomized interventional studies; SD: Standard Deviation; PO: Oral; IM: intramuscular; Top: Topical; NS: Not specified; mo(s): month(s); w(s): week(s); T: Testosterone; HCG: Human chorionic gonadotropin; DHT: Dihydrotestosterone; TIP: Tubularized incised plate; pts: patients; Mean age and its standard deviation is expressed in years otherwise specified.

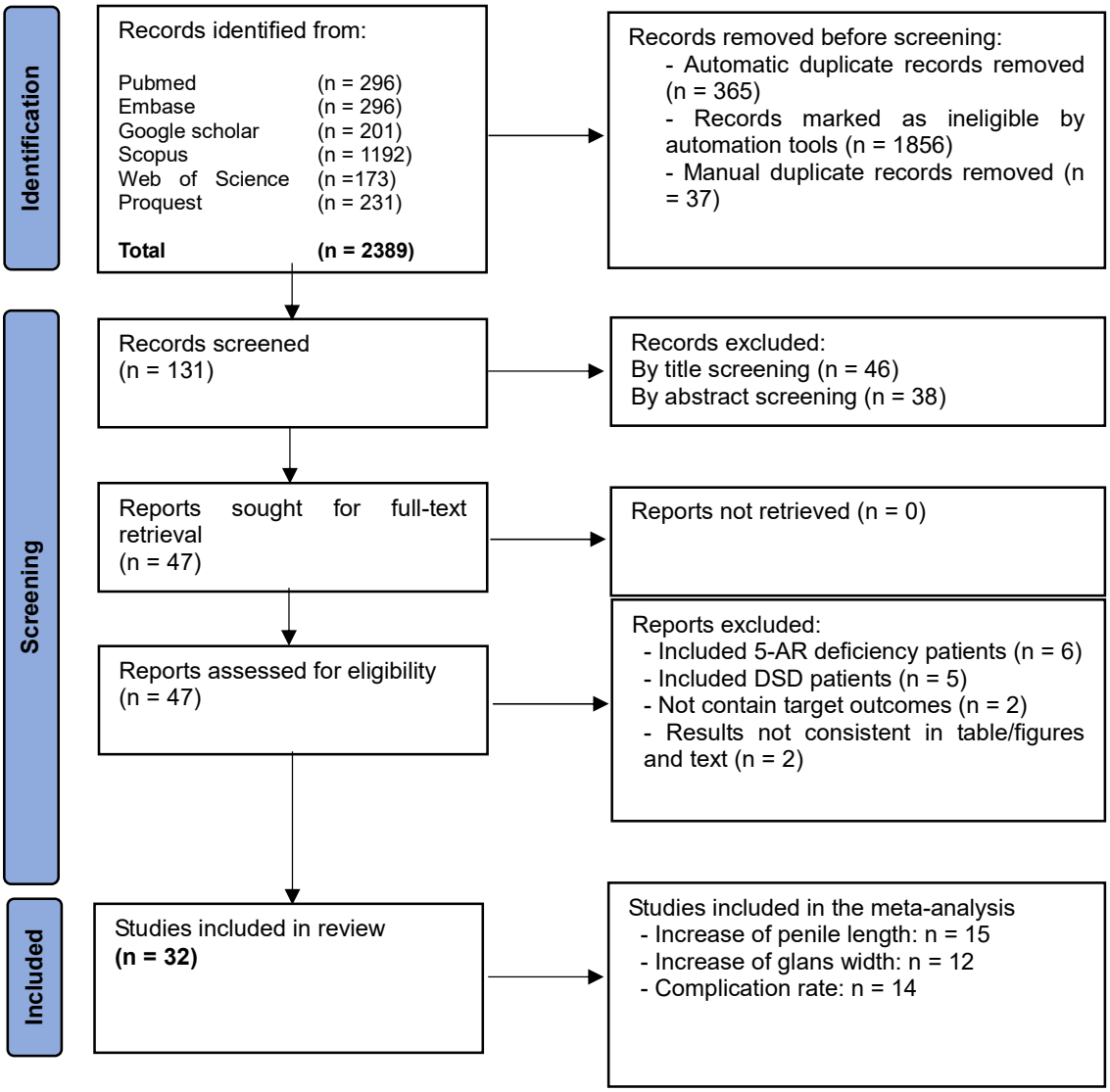


Figure 1. The PRISMA flow diagram of the included studies. DSD: disorders of sexual differentiation.

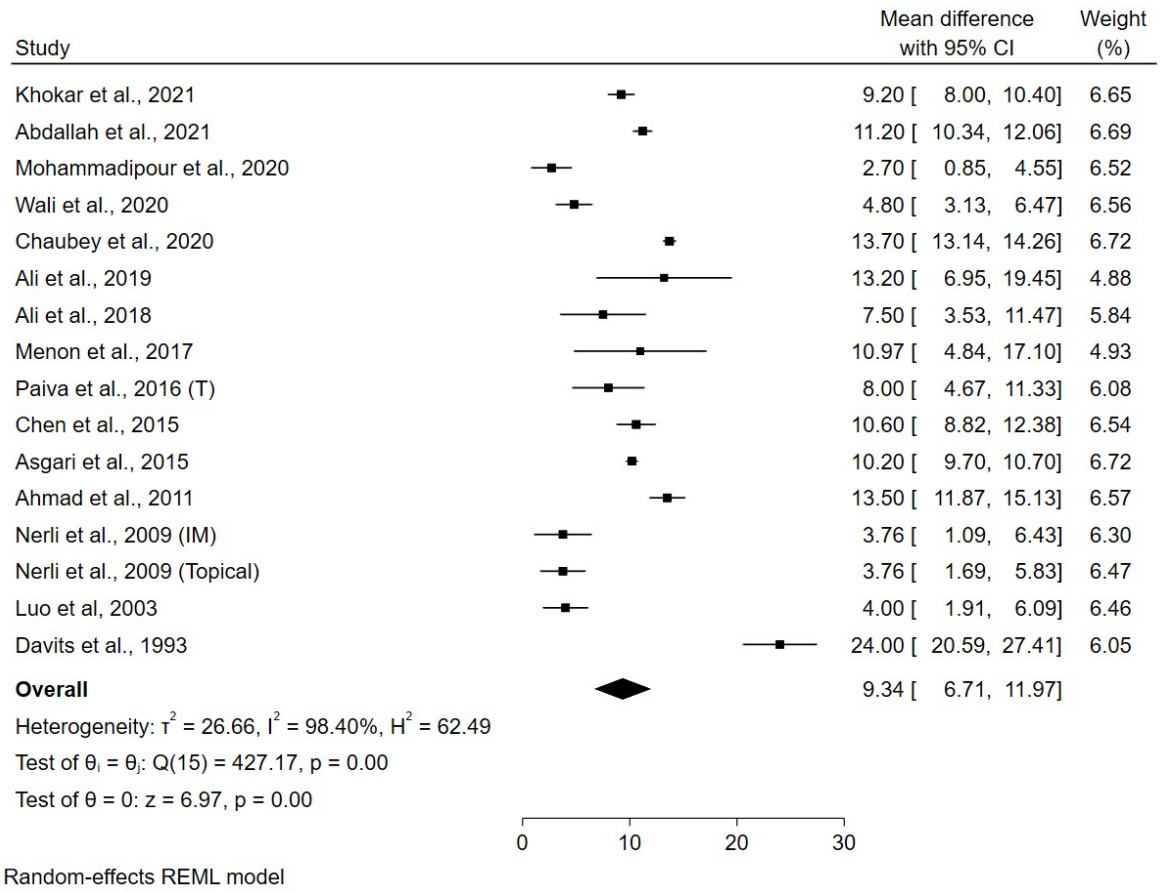


Figure 2. Forest plot showing the increase of penile length after preoperative testosterone stimulation (15 studies)

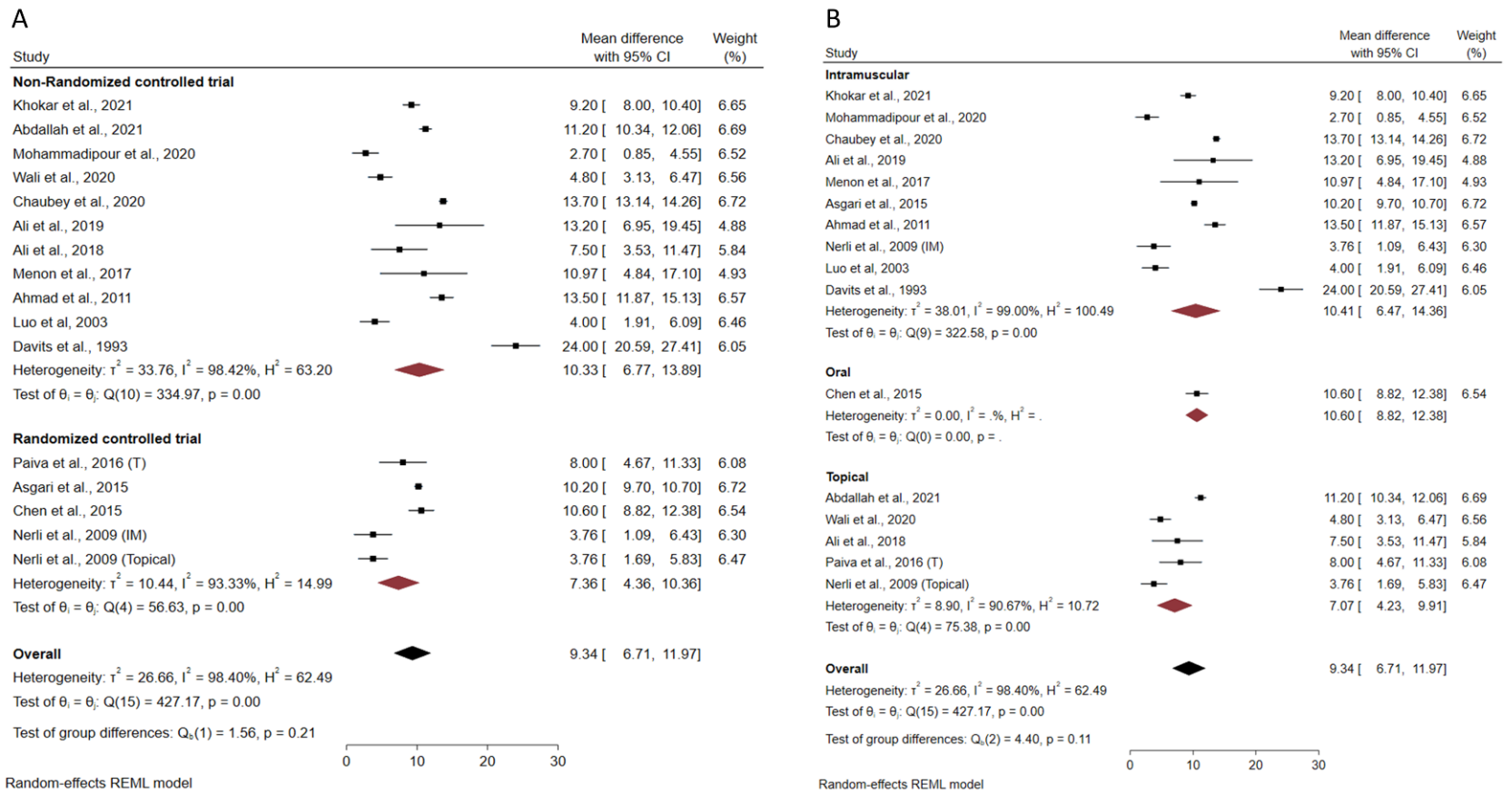


Figure 3. Forest plot showing the increase of penile length after preoperative testosterone stimulation (15 studies), **A**: subgroup analysis by study design, **B**: subgroup analysis by delivery route

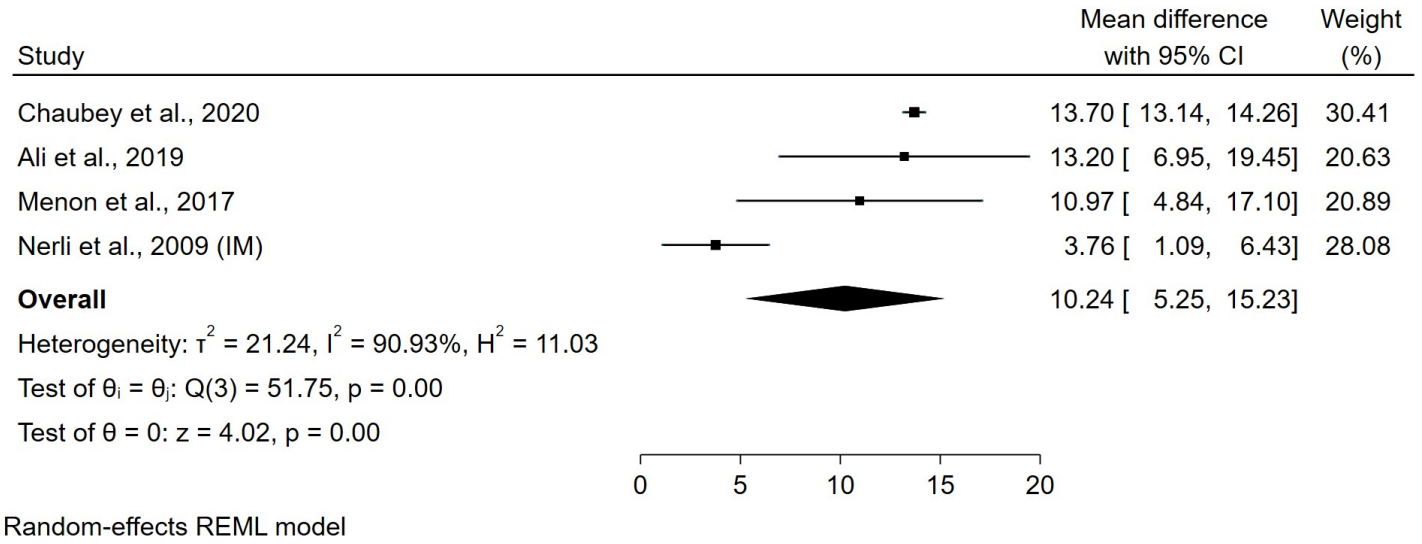


Figure 4. Forest plot showing the increase of penile length after preoperative testosterone stimulation with the same protocol: intramuscular testosterone, 2 mg/kg, once a month for three months.

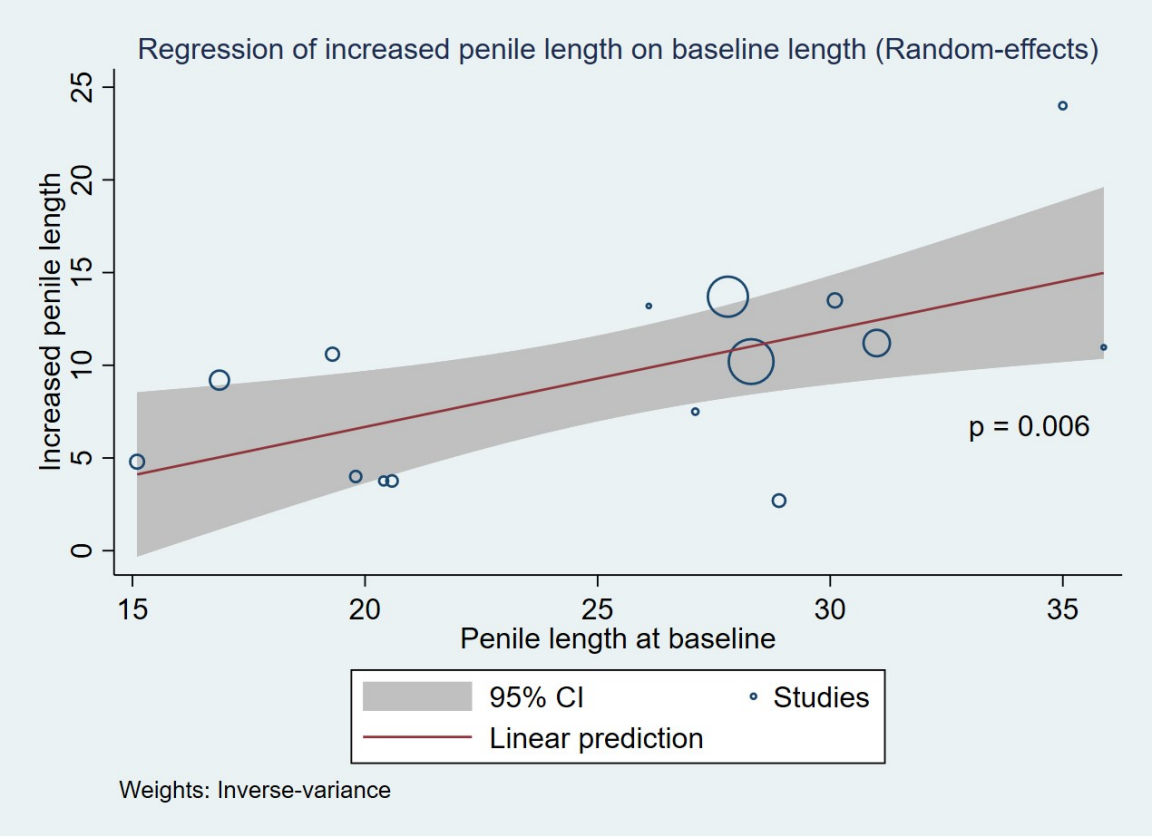


Figure 5. Bubble plot of the increased penile length against pretreatment penile length. Each study is represented by a bubble, with the sizes of the bubbles proportional to the weight assigned to the studies: the larger the weight, the larger the bubble. The line represents the association between the increased penile length and the penile length at baseline.

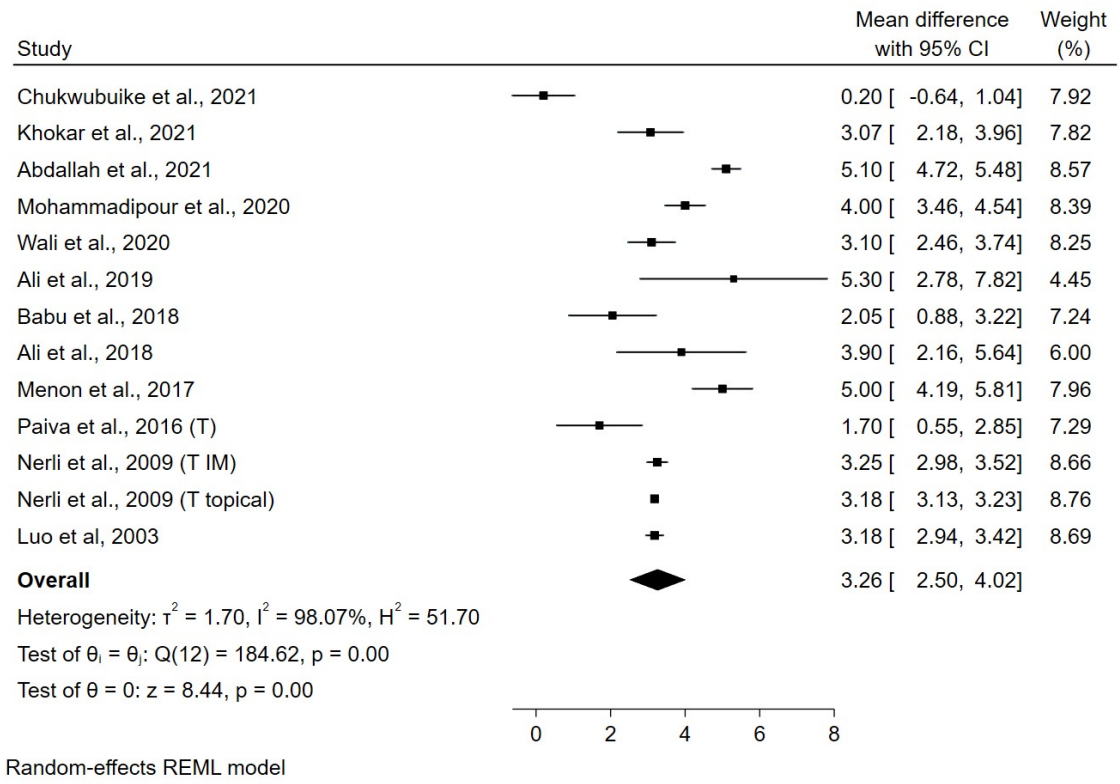


Figure 6. Forest plot showing the increase of glans width after preoperative testosterone stimulation (12 studies)

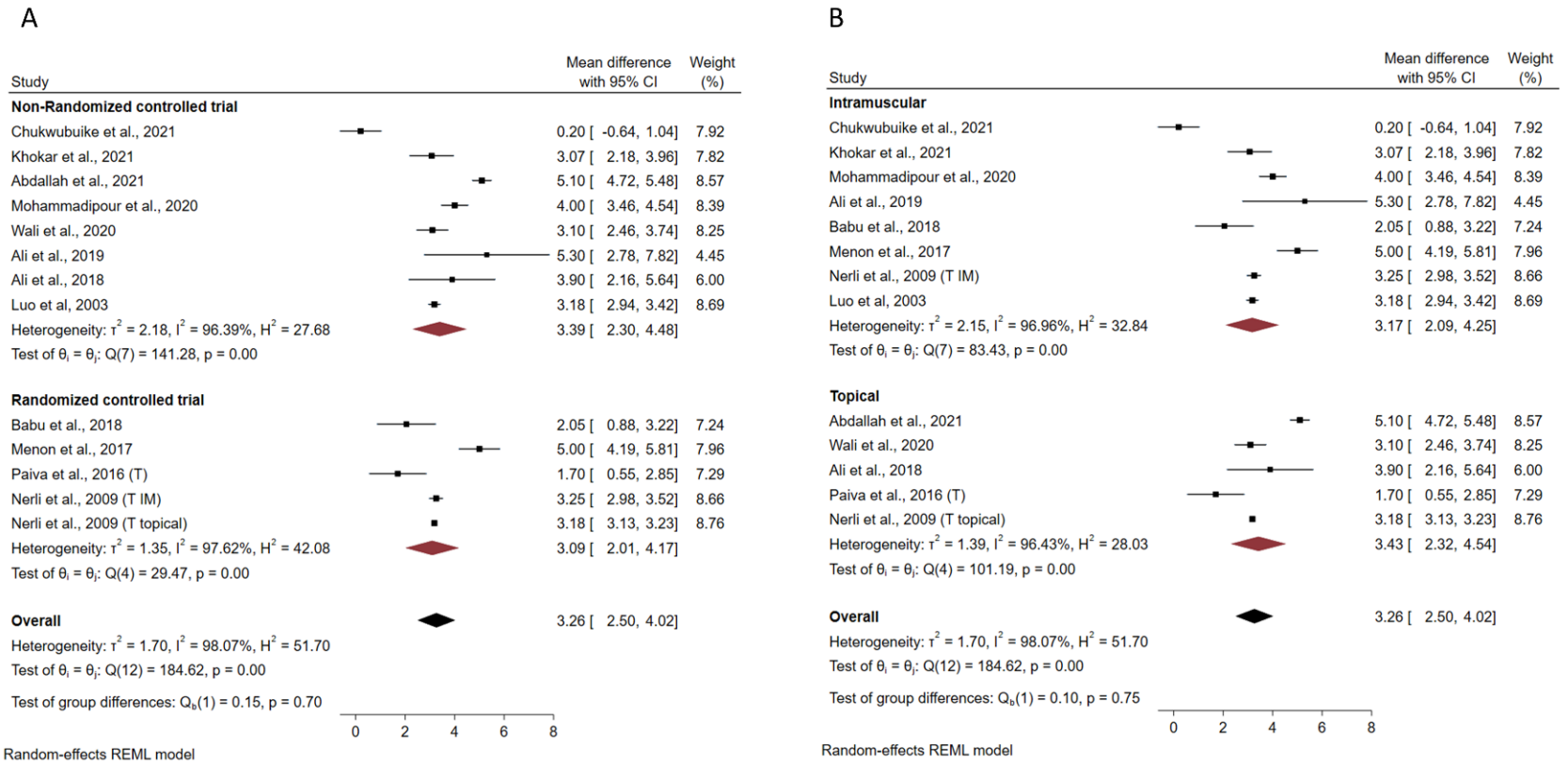


Figure 7. Forest plot showing the increase of glans width after preoperative testosterone stimulation (12 studies), **A**: subgroup analysis by study design, **B**: subgroup analysis by delivery route

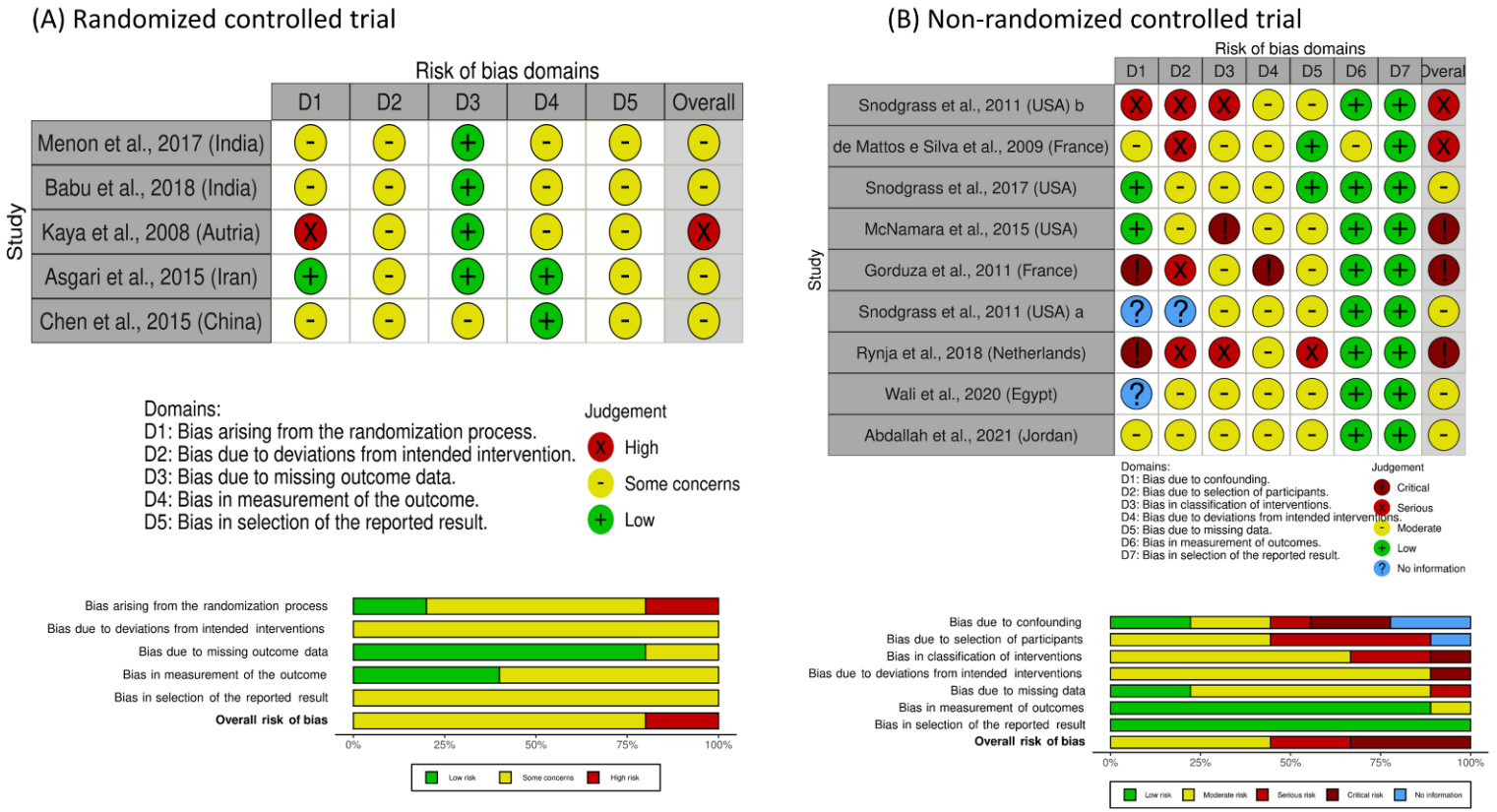
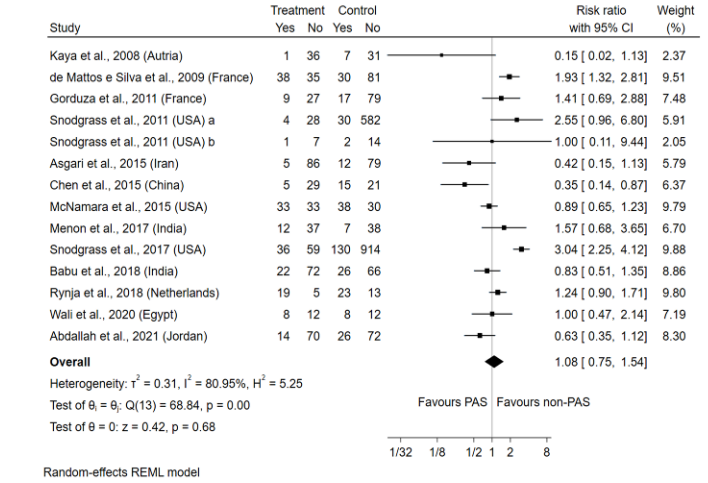
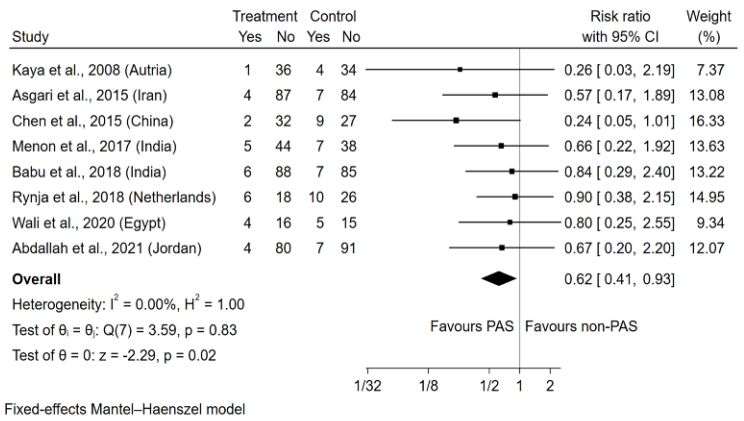


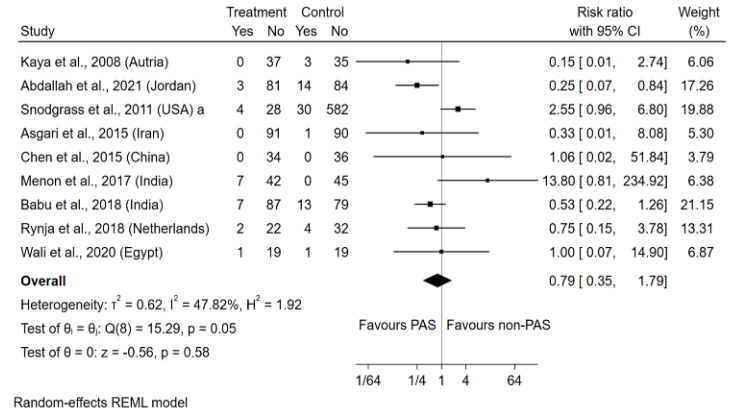
Figure 8. Risk of bias assessment for **A**: randomized control trials (5 studies) and **B**: non-randomized control trials (9 studies)



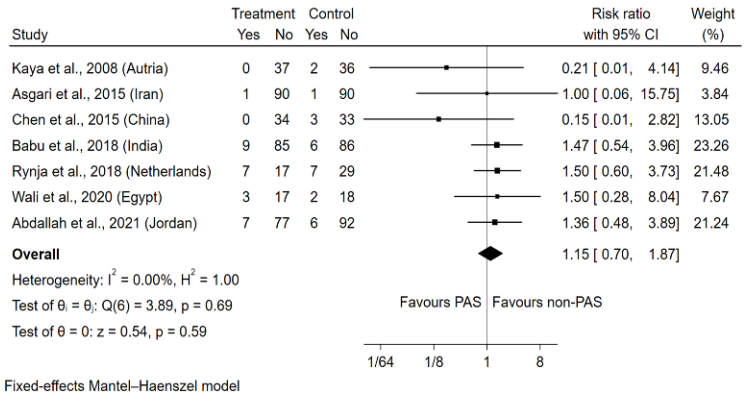
(A) Risk of overall postoperative complication



(B) Risk of postoperative fistula



(C) Risk of postoperative wound dehiscence



(D) Risk of postoperative stenosis

Figure 9. Forest plot showing the risk of postoperative complication of hypospadias repair between PAS versus non-PAS patients (14 studies). Fig.5A, overall complication; Fig.5B, fistula; Fig. 5C, wound dehiscence; Fig 5C, urethral stenosis

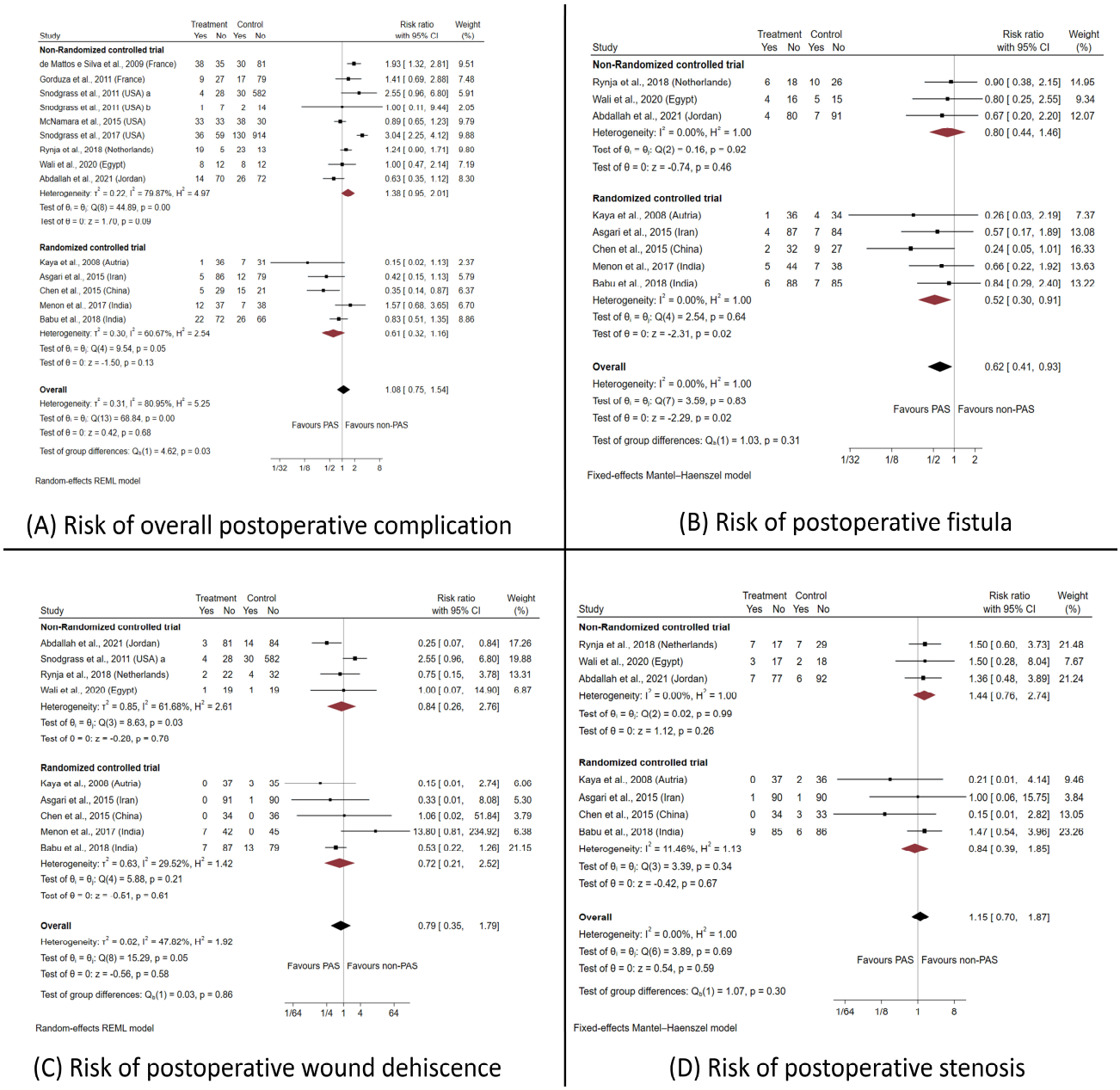


Figure 10. Forest plot showing the risk of postoperative complication of hypospadias repair between PAS versus non-PAS patients, subgroup analysis by study design (14 studies). Fig.6A, overall complication; Fig.6B, fistula; Fig. 6C, wound dehiscence; Fig 6C, urethral stenosis

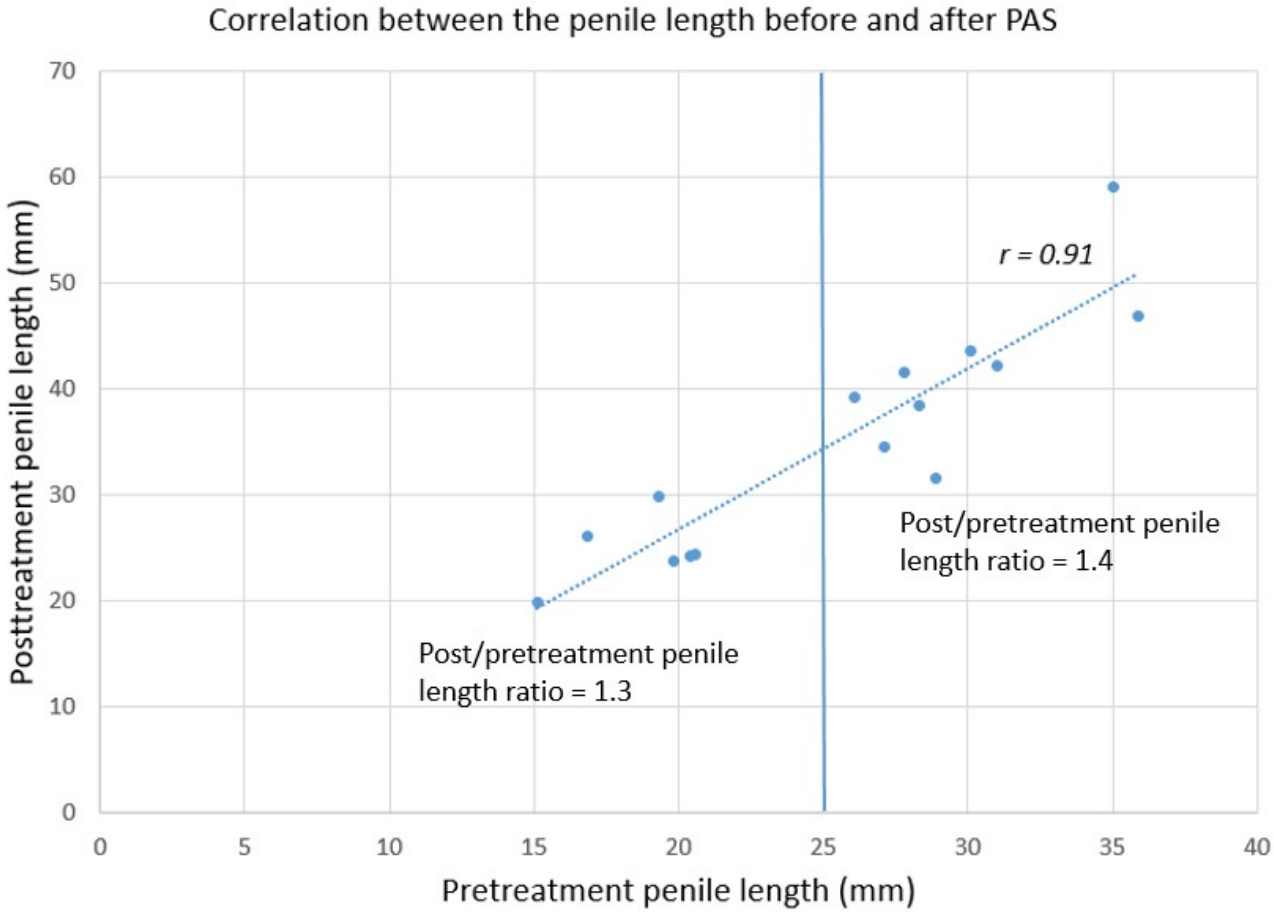


Fig. 11. Correlation between the penile length before and after PAS

The scatter plots show the correlation between penile length before and after preoperative androgen stimulation (PAS), the regression line (dotted line), and the correlation coefficient r. The solid line divides the pretreatment penile length into two groups with a cut-off at 25 mm. The post/pretreatment penile length ratio of each group is shown.

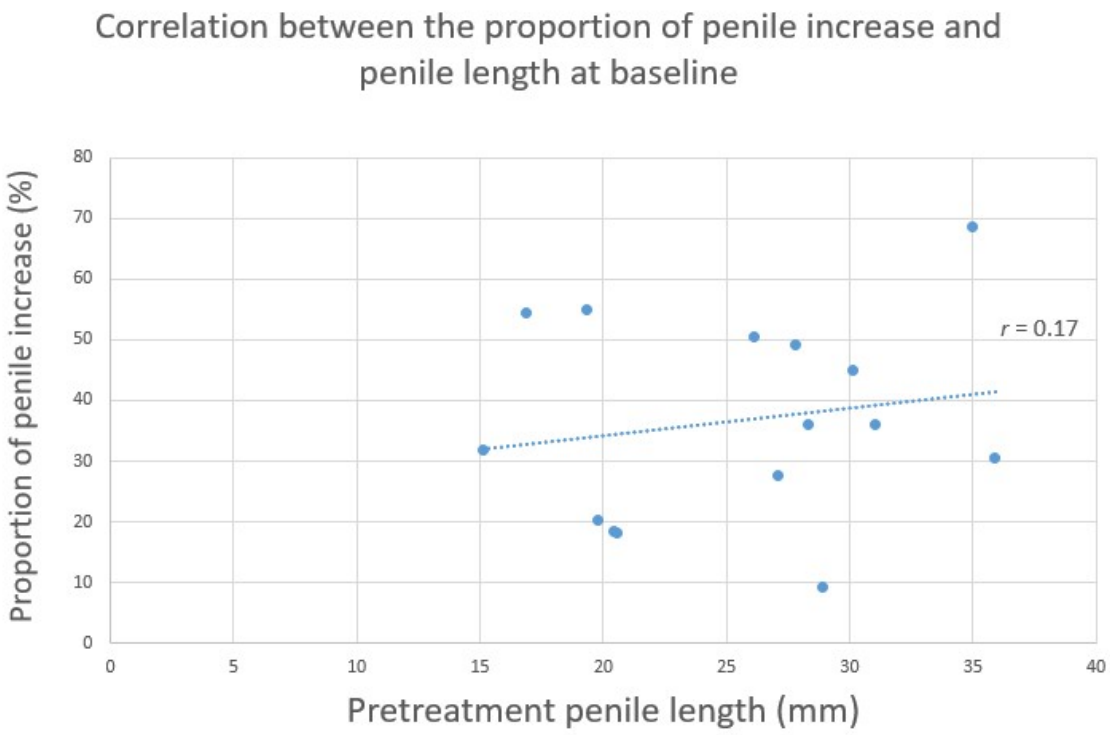


Fig. 12. Correlation between the proportion of penile increase and penile length at baseline

The scatter plots show the correlation between penile length before preoperative androgen stimulation and the proportion of penile increase (penile increase/ penile length before treatment), the regression line (dotted line), and the correlation coefficient *r*.

Appendix

The formulas for conversion and imputation of missing mean difference and standard deviation

1. Conversion from median to mean: using online calculator. [1]

Available at https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html

2. Conversion between standard deviation (SD) and standard error (SE):

$$\mathrm{SD} = \mathrm{SE} \times \sqrt{N}$$

N: sample size

3. The confidence interval for a mean can also be used to calculate the SD [2]

$$\mathrm{SD} = \sqrt{N} \times (\text{upper limit} - \text{lower limit}) / 3.92$$

N: sample size

4. Imputing SD for changes from baseline

1) If the t-value was provided, SD was calculated using following equation [3]

SD = (MD/t) x sqrt(N)

Where: MD is mean difference, t: t-value, sqrt: square root, N: sample size

2) If the t-value was not available, the following method was used to impute the SD [2]

	Baseline	Final	Change
Experimental intervention (sample size N_E)	$M_{E,\text{baseline}}$, $\mathrm{SD}_{E,\text{baseline}}$	$M_{E,\text{final}}$, $\mathrm{SD}_{E,\text{final}}$	$M_{E,\text{change}}$, $\mathrm{SD}_{E,\text{change}}$
Comparator intervention (sample size N_C)	$M_{C,\text{baseline}}$, $\mathrm{SD}_{C,\text{baseline}}$	$M_{C,\text{final}}$, $\mathrm{SD}_{C,\text{final}}$	$M_{C,\text{change}}$, $\mathrm{SD}_{C,\text{change}}$

M: mean; E; Experimental intervention; C: Comparator intervention

The correlation coefficient in the experimental group, $Corr_E$, can be calculated as:

$$\mathrm{Corr}_E = \frac{\mathrm{SD}^2_{E,\mathrm{baseline}} + \mathrm{SD}^2_{E,\mathrm{final}} - \mathrm{SD}^2_{E,\mathrm{change}}}{2 \times SD_{E,\mathrm{baseline}} \times SD_{E,\mathrm{final}}}$$

Imputing a change-from-baseline standard deviation using a correlation coefficient. There was heterogeneity in calculated correlation efficient. Accordingly, the correlation was conservatively set at 0.5 as previously reported [4].

$$\mathrm{SD}_{E,\mathrm{change}} = \sqrt{\mathrm{SD}^2_{E,\mathrm{baseline}} + \mathrm{SD}^2_{E,\mathrm{final}} - \left(2 \times \mathrm{Corr} \times \mathrm{SD}_{E,\mathrm{baseline}} \times \mathrm{SD}_{E,\mathrm{final}}\right)}$$

5. Combining groups: In case the sample was devided in to 2 sub-groups, mean and SD was calculated using following formula [2].

Formulae for combining summary statistics across two groups: Group 1 (with sample size = N_1, mean = M_1 and SD = SD_1) and Group 2 (with sample size = N_2, mean = M_2 and SD = SD_2)

	Combined groups
Sample size	$N_1 + N_2$
Mean	$\frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$
SD	$\sqrt{\frac{(N_1 - 1)\mathrm{SD}_1^2 + (N_2 - 1)\mathrm{SD}_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$

References for appendix

1. Wan X, Wang W, Liu J, Tong T: Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014, 14:135.

2. Higgins JPT, Li T, JJ D: Chapter 6: Choosing effect measures and computing estimates of effect. In: Cochrane Handbook for Systematic Reviews of Interventions version 63 (updated February 2022). Edited by Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA: Cochrane; 2022: Available from www.training.cochrane.org/handbook.

3. Sutton AJ, Abrams KR, Jones DR, Jones DR, Sheldon TA, Song F: Methods for meta-analysis in medical research, vol. 348: Wiley Chichester; 2000.

4. Follmann D, Elliott P, Suh I, Cutler J: Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol 1992, 45(7):769-773.

수술 전 안드로겐 자극이 요도하열 환자의 음경 크기 및 수술 후 합병증 발생률에 미치는 영향: 체계적인 문헌 고찰 및 메타 분석

목적: 요도하열이 있는 환자에서 수술 전 안드로겐 자극(preoperative androgen stimulation; PAS)이 음경길이와 귀두너비에 미치는 정량적증가의 범위를 규정하고 수술 후 각각의 합병증에 미치는 효과를 메타 분석의 방법으로 체계적으로 고찰하고 평가하고자 했다.

재료 및 방법: Pubmed, Embase, Google Scholar, Scopus, Web of Science 및 Proquest에서 1980년에서 2022년 사이에 출판된 문헌에 대한 포괄적인 검색이 수행되었다. 5알파 환원효소 결핍증, 성분화장애, 요도하열이 없는 왜소음경이 있는 환자에 대한 연구는 제외되었다. 본문 검토, 문헌의 질 평가 및 데이터 수집은 두 명의 검토자가 독립적으로 수행했다. 음경 성장의 정량화와 수술 후 합병증발생의 증가여부를 판단하기 한 메타분석이 수행되었다.

결과: 초기 문헌 검색에서 2,389건의 문헌이 검색되었으며, 이 중 32건의 연구가 체계적인 문헌 고찰 및 메타 분석에 적합했다. 수술 전 테스토스테론 자극은 음경길이와 귀두너비를 각각 9.34 mm (95% CI: 6.71–11.97) 및 3.26 mm (95% CI: 2.50–4.02) 증가시켰다. 치료전에 더 긴 음경 일 수록 치료 후 더 큰 길이 증가로 이어졌다. 치료전에 음경이 1mm 더 길었던 환자에서 0.5mm 더 늘어날 가능성이 있었다. 그러나 음경길이의 증가는 요도하열 의 중증도와 관련이 없었다. 치료가 전체

합병증 발생률에 영향을 미치지는 않았지만, 수술 후 누공 위험은 PAS를 받은 그룹에서 통계적으로 유의하게 더 낮았다 (RR = 0.52, 95% CI: 0.30–0.91, p = 0.02).

결론: PAS의 음경길이 및 귀두너비 증가에 대한 유익한 효과가 다시 확인되었다. 치료 전에 더 큰 음경에서 더 많은 음경길이 증가가 예상되었다. PAS와 관련된 수술 후 합병증의 증가는 보고되지 않았다.

키워드: 요도하열; 메타 분석; 수술 전 안드로겐 자극; 수술 후 합병증; 테스토스테론.

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