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VIEWPOINT

Defining the role of pre-operative hormonal therapy in hypospadias

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In hypospadias surgery, pre-operative hormonal therapy (PHT) is primarily used to increase penile dimensions and the vascularity of tissues available for reconstruction, but its use is non-uniform in clinical practice, with no consensus on application or utility. This review aims to summarise: (i) the penile tissue response to hormone therapy, (ii) its impact on hypospadias surgery outcomes, and (iii) the endocrinological considerations and sequelae. PHT is more often indicated for complex cases such as proximal hypospadias, hypospadias with microphallus and hypospadias reoperations. While PHT has clear effects on penile morphometry, and more recent controlled trials suggest improved surgical outcomes, the lack of consistent outcome definitions and generally inadequate follow-up periods continue to consign many of the potential long-term effects of PHT to the unknown. There is currently insufficient robust evidence to allow a clinical guideline to be constructed. The need for a well-powered multi-centre prospective randomised trial to address this question is evident but awaits a unified consensus on issues surrounding the understanding of aetiology, classification of hypospadias morphology, definition of important prognostic variables and uniform application of outcome measures. The effects of PHT may be utilised to improve outcomes in cases of proximal and severe hypospadias, which under the current paradigm represent a significant surgical challenge.

Key words: hypospadias; hormone therapy; testosterone; dihydrotestosterone; androgens.

The use of pre-operative hormonal therapy (PHT) in hypospadias surgery was first explored in the 1970s.[1] There is diverse international practice regarding the application of PHT (Table 1), highlighting the need for thorough consideration of the evidence-base when caring for these children. The current review aims to clearly summarise the evidence for paediatric urologists, endocrinologists, and other clinicians involved in the care of children with hypospadias. This review covers three sections: (i) the penile tissue response to hormone therapy, (ii) its impact on hypospadias surgery outcomes, and (iii) the endocrinological considerations and sequelae.

Pre-operative testosterone has been primarily used to increase penile length, glans width/circumference, inner preputial area, and the vascularity of tissues available for reconstruction in more complex cases such as proximal hypospadias, or hypospadias with co-existing small glans or penis.[7]

Defining proximal hypospadias is problematic as some surgeons classify this based on the level of division of the corpus spongiosum in the degloved penis, which can only be defined intra-operatively.[8] Significant heterogeneity exists across studies regarding both pre-operative androgen type, dose and treatment timing. The most frequently reported preparations are intramuscular (IM) testosterone, and topical testosterone or dihydrotestosterone (DHT).[4,6] The most frequently reported regimens for IM testosterone esters are either 2 mg/kg or empiric 25 mg monthly, for 2–3 months pre-operatively.[4,6,9,10] Some authors contend that DHT may be more effective as it does not rely on 5-alpha reductase conversion of testosterone,[11] and aberrations in 5-alpha reductase activity have been variably associated with hypospadias.[12,13]

A large international study surveying 377 surgeons across 68 countries reported variable PHT use: 68.2% rarely, 10.9% regularly and 1.9% always.[6] Most respondents favoured either IM testosterone (43.8%) or topical DHT (39.4%); with smaller numbers using topical testosterone (15.7%) and IM β-hCG (1.1%). A further survey by the American Academy of Paediatrics evaluated a small group of surgeons, and the overall rate of pre-operative testosterone use was 78%.[4] The most used agent was IM testosterone (67%). Many respondents (55%) were high-volume surgeons performing >50 hypospadias procedures annually, and higher rates of PHT were reported in high-volume versus low-volume surgeons (87% vs. 67%).

Penile Tissue Response to Hormone Therapy

PHTis more often considered when a complex hypospadias repair is anticipated (e.g. in proximal hypospadias, or hypospadias with

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Table 1 International practice surveys of pre-operative hormone therapy prior to hypospadias repair

Country (year)	Surgeons surveyed	Practice includes PHT (%)	Main criteria for use of PHT	Most commonly used agent
Nigeria (2020)[2]	50	77%	92.1% for small penis 86.8% for proximal hypospadias	76.3% IM testosterone (2 mg/kg)
Turkey (2016)[3]	99	44% 91% (proximal hypospadias)	Small penis Reduced glans circumference Ambiguous genitalia	56.8% topical DHT 15.6% IM β-hCG 13.7% Other
USA (2014)[4]	27	87%	70% for reduced glans circumference 51% for proximal hypospadias 48% for small penis	67% IM testosterone 29% topical testosterone
International: 82% from UK and Europe (IVth World Congress of the International Society on Hypospadias and Disorders of Sex Development Meeting 2011)[5]	93 (including 52 non-surgical delegates)	79%	Survey did not ask for specific indications	IM or topical preparations
International: 68 countries included (2011)[6]	377	68.2% rarely 10.9% regularly 1.9% always	Survey did not ask for specific indications	43.8% IM testosterone 39.4% topical DHT 15.7% topical testosterone 1.1% β-hCG

β-hCG, beta-human chorionic gonadotropin; DHT, dihydrotestosterone; IM, intramuscular.

co-existing small penis/glans (microphallus)). PHT increases penile and glanular size and optimises preputial vascularity; however, these changes may not be sustained.[14–18] Increasing glanular and penile tissue may assist ventral closure of the neourethra and glans in more complex cases. Improved vascularity of local tissues may be beneficial to wound healing and aid in achieving a tension-free repair. The reported tissue benefits of PHT (Table 2) suggest the potential to improve surgical outcomes and reduce complications.

Increase in glans width or circumference

Glans width measurement in the outpatient setting differs from intraoperative measurement after preputial adhesions are divided, with overestimation occurring in the clinic.[25] Nonetheless, many studies have shown significant increases in glans width or circumference following PHT (with both IM[17,20,21,25,27] and topical testosterone[17,22]). A more limited response was seen in distal hypospadias (17%)[20] compared with proximal hypospadias (57%).[25] There was a greater increase in glans width in those aged less than 5 years (3.9 mm), compared to those 5 years and older (2.4 mm), indicating that younger patients may be more responsive to PHT.[21] Statistically significant increases have been demonstrated following both IM and topical testosterone.[35] Several studies have also noted an increase in penile base circumference.[19,22–24,30,32–34]

Increase in penile length

Several studies suggest PHT is effective for increasing both stretched[19,22–24,29,36] and unstretched penile length.[17,21,26–28,30–34] This effect has been noted for IM testosterone,[17,21,24,26–28,30,32] topical testosterone,[17,19,22,28,31,33] topical DHT,[34] oral testosterone,[23] and parenteral hCG.[29] No change in penile biometry was noted with topical estradiol.[22]

Two prospective cohort studies directly compared IM and topical testosterone preparations in children with microphallic hypospadias. One study suggested a lower rate of penile enlargement with topical treatment (60% vs. 75%), although this was not statistically significant.[28] Overall, studies suggest equivalent results with both IM and topical testosterone for increasing penile length.[17,28,35]

The value of some studies is limited by the quality of the control groups and a lack of standardised or reproducible measurements. For example, a study of 17 boys with proximal and distal hypospadias found that treatment with IM testosterone enanthate significantly increased penile length by 1.1 ± 0.5 cm ($P < 0.001$),[26] but this was compared to a control group of non-hypospadiac microphallus patients. In a similar study of 25 microphallic hypospadias cases, increases in penile morphometry were seen but the study lacked a control arm altogether.[27] In another study, a definitive increase in overall penile size, available penile skin and local vascularity following topical testosterone was noted; however, none of these outcomes were measured objectively.[31] Earlier studies also lacked sufficient statistical analysis to confirm the significance of reported results.[32–34]

The effect of PHT on penile length and size may not be maintained over time. An early study suggested a loss of size subsequent to PHT of 'approximately 50%' after 1 year.[34] This was corroborated by a Dutch study showing penile length reduced by 17% from its peak at 12-month post-operatively[30] (Fig. 1). A randomised study looking at both distal and mid-shaft hypospadias demonstrated a progressive increase in penile length on stopping treatment, with increases in penile length of 22%, 35%, and 36% at 1-, 2-, and 3-month post-injection, respectively.[24] Based on these findings, the greatest tissue response, at least in terms of penile length, appears to be at 3 months following PHT.

Table 2 Studies of tissue response to pre-operative hormone therapy

Country (year)	Design	Patient group (*N*)	Exposure	Outcome
India (2020)[19]	RCT	Distal hypospadias (42)	1% testosterone propionate ointment 1 month prior to surgery	Increase in SPL (42%, $P < 0.001$). Increase in transverse preputial width (42%, $P < 0.001$). Increase in diameter of penis at base (80%, $P < 0.001$).
India (2018)[20]	RCT	Distal hypospadias (186)	2 mg/kg testosterone enanthate (IM) monthly ×3 EG ($n = 94$) CG ($n = 92$, hypospadiac)	Increase in glans width in responders (12.9–15.3 mm, $P = 0.001$). Overall, 83% were responders and 17% non-responders in the treatment arm.
India (2017)[21]	RCT	Distal hypospadias (94)	2 mg/kg testosterone enanthate (IM) monthly ×3 EG ($n = 49$) CG ($n = 45$, hypospadiac)	Penile dimensions of length, base circumference and glans width all increased significantly following testosterone ($P < 0.001$).
Brazil (2016)[22]	Double-blind RCT	Hypospadias (69)	EG1 – 1% testosterone propionate ointment ($n = 28$) EG2 – 0.01% oestradiol ointment ($n = 24$) CG ($n = 17$, hypospadiac) Applied topically BD 1 month prior to surgery	EG1: Increase in SPL ($P < 0.001$), diameter of the penis at its base ($P < 0.001$), and glans diameter ($P < 0.001$). EG2: No change in biometric aspects of the penis.
China (2015)[23]	RCT	Primary proximal hypospadias repair with microphallus – <2.5 SD below normal (72)	Oral testosterone undecanoate 2 mg/kg/day for 3 months *or* until microphallus resolved EG ($n = 36$) CG ($n = 36$, hypospadiac)	SPL increased by 1.1 cm ($P = 0.001$) and penile diameter by 0.3 cm ($P = 0.001$).
Iran (2015)[24]	RCT	Midshaft or distal hypospadias with flat urethral plates (182)	2 mg/kg IM testosterone enanthate monthly for 2 months, 1 month before surgery EG ($n = 91$) CG ($n = 91$, hypospadiac)	SPL and circumference were significantly increased among the hormone exposed group compared with controls. SPL increased from 28.3 to 38.4 mm ($P = 0.001$). Penile circumference increased from 35.3 to 45.5 mm ($P = 0.001$).
USA (2014)[25]	Non-randomised controlled trial	Mid-shaft and proximal hypospadias (62)	Testosterone cypionate IM in those with glans width < 14 mm – initially 2 mg/kg 2–3 monthly, if glans width not considered satisfactory escalating monthly doses (4, 8, 16 mg/kg, etc.). Midshaft hypospadias – EG ($n = 5$) – CG ($n = 10$, hypospadiac) Proximal hypospadias – EG ($n = 29$) – CG ($n = 18$, hypospadiac)	5/15 mid-shaft cases treated – mean initial glans width 11.6 mm, increased to mean 16 mm after 2–3 doses. 23/47 proximal cases initially treated – mean initial glans width 11.1 mm, 57% did not reach target glans width and required escalating doses.

(*Continues*)

Table 2 (Continued)

Country (year)	Design	Patient group (*N*)	Exposure	Outcome
Brazil (2011)[14]	RCT	Hypospadias (26)	1% testosterone propionate ointment twice daily for 30 days before surgery. EG ($n = 13$) CG ($n = 13$, hypospadiac)	Preputial neovascularisation: Testosterone-treated prepuces had increased absolute number of blood vessels ($P < 0.001$) and increased blood vessel volume density ($P < 0.001$).
Japan (2010)[26]	Prospective cohort study	Hypospadias (17)	25 mg testosterone enanthate IM. The injection was repeated every 4 weeks up to three times until penile length was above mean age-matched references. Compared with age-matched micropenis (non-hypospadiac) patients.	Penile length significantly increased by 1.01 ± 0.50 cm and 2.27 ± 0.99 SD (cm, $P = 0.0002$; SD, $P = 0.0002$).
India (2009)[17]	Prospective cohort study	Hypospadias with microphallus (21)	Randomised to either: – Testosterone cream (2 mg/kg/week) over 3 weeks ($n = 10$) – Testosterone enanthate IM 2 mg/kg monthly for 3 months pre-operatively ($n = 11$)	Increase in penile length and glans circumference following testosterone therapy in both topical and parenteral groups (all P values < 0.05).
Taiwan (2003)[27]	Prospective cohort study	Hypospadias with microphallus (25)	Testosterone enanthate 25 mg IM monthly, up to ×3, pre-operatively	Increased penile length (19.8–23.8 mm, $P < 0.001$). Increased glans circumference (27.4–37.84 mm, $P < 0.001$).
India (2003)[28]	Prospective cohort study	Hypospadias with microphallus (25); epispadias (1)	Either: – Testosterone enanthate + propionate oil (2 mg/kg/week) for 3 weeks ($n = 13$) – Testosterone enanthate 2 mg/kg IM weekly, for 3-week pre-operatively ($n = 13$)	Increased (unstretched) penile length post-therapy in both topical (2.0–3.18 cm) and parenteral (1.8–3.11 cm) groups ($P < 0.01$). Rate of penile enlargement less in topical group (60%) versus parenteral (75%), but difference not significant ($P > 0.1$).
USA (1999)[29]	Prospective cohort study	Proximal hypospadias with chordee (12)	hCG twice weekly injection for 5 weeks, 6–8 weeks pre-operatively Dosing: – 250iU (<1 year old) – 500iU (1–5 years old)	Increase in SPL in all cases following hCG (mean increase of 94%, $P < 0.001$). Increase in distance between penoscrotal junction and meatus (3.2–14.4 mm, $P < 0.001$). Change in distance between meatus and glans tip post-hCG minimal and not statistically significant. Subjective increase in quantity of preputial and penile shaft skin, vascularity of corpus spongiosum, and decrease in severity of chordee also noted.
The Netherlands (1993)[30]	Prospective cohort study	Hypospadias (40)	Testosterone enanthate + propionate depot (2 mg/kg) IM 5 and 2 weeks pre-operatively	Increased mean unstretched penile length (from 3.5 to 5.9 cm, $P < 0.001$). Increased penile base circumference (32%, $P < 0.01$). Increased transverse length of inner preputial area (58%, $P < 0.01$).

(*Continues*)

Table 2 (Continued)

Country (year)	Design	Patient group (*N*)	Exposure	Outcome
				Penile length at 6- and 12-month post-operatively diminished to 4.4 and 4.9 cm.
Japan (1991)[31]	Prospective cohort study	Hypospadias (15)	Testosterone ointment (0.2–0.4 g) once daily, for 3 weeks, then 1-week break. Repeated for at least 3 cycles.	Subjective increase in overall penile size, available penile skin and local vascularity in all cases.
USA (1987)[32]	Prospective cohort study	Hypospadias (36), epispadias (5), urethral fistulas (3)	Testosterone enanthate 2 mg/kg IM, 5- and 2-week pre-operatively	Mean increase in penile length (2.7 cm) and penile circumference (2.3 cm) following testosterone (not statistically analysed). Increased local vascularity and penile skin availability subjectively reported.
Israel (1983)[33]	Prospective cohort study	Hypospadias with microphallus (7)	10% testosterone propionate cream, twice daily for 3 weeks	Increased dorsal penile length (range 18–27 mm pre; 30–36 mm post) Increased ventral penile length (range 15–23 mm pre; 28–32 mm post) Increased penile base diameter (range 12–15 mm pre; 16–19 mm post) [no statistical analysis]
France (1982)[34]	Prospective cohort study	Hypospadias (45) and epispadias (5)	DHT cream (0.6 g/day for ages <10 years, 1 g/day for 10–15 years) once daily, for 1-month pre-operatively	'Impressive' increase in penile length and circumference following therapy in 75% of cases. Average loss of size ~50% after 1 year. Subjective increase in local hypervascularity/hyperaemia [nil statistical analysis].

CG, control group; DHT, dihydrotestosterone; EG, exposure group; hCG, human chorionic gonadotropin; SPL, stretched penile length.

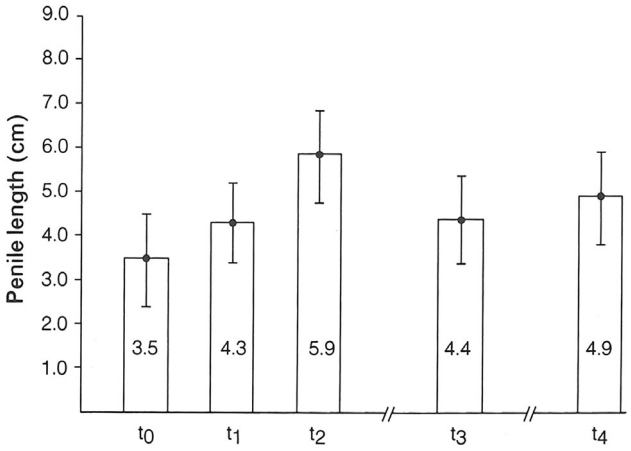

Fig. 1 Mean stretched penile length before treatment with testosterone IM (2 mg/kg) labelled (t_0). The first testosterone was given 5-weeks pre-operatively. Three-weeks following this a further dose was given and measurements taken (t_1). Surgery was performed 2-weeks following this and further measurements taken (t_2). Further stretched penile measurements were obtained 3- (t_3) and 12- (t_4) months post-operatively. Image reproduced with permission.[30]

Other biometric effects on the penis

One study of PHT in children with proximal hypospadias observed significant, but disproportionate, penile lengthening that moved the urethral meatus distally, with all of the increase in penile length occurring proximal to the ectopic meatus.[29] A reduction in chordee severity was also noted.[29] These findings suggest that there is good growth of all the tissues around the hypospadiac plate (glans, corpora, proximal urethra, etc.), while the urethral plate itself is less affected by PHT.

It is noteworthy that penile length and base circumference increase by approximately 30%, but glans width increases comparatively less following PHT (16.5%).[21] Preputial skin is utilised in many types of hypospadias repair and is seen to increase following PHT. Gearhart and Jeffs[32] saw the mean transverse prepuce length increase from 3.0 to 5.0 cm following parenteral testosterone, but no statistical analysis was performed. The transverse inner prepuce length was confirmed to increase by 58% ($P < 0.01$) following parental testosterone in a subsequent study.[30] Increased preputial skin was also subjectively reported following hCG treatment.[29]

Neovascularisation of the penile soft tissues

The importance of preputial vascularity in hypospadias surgery lies in the many ways the prepuce may be used in reconstruction. Local increases in vascularity following PHT have been subjectively reported in several historical studies.[31,32,34] In a transplant model, full-thickness human paediatric prepuces receiving a single treatment of 1% testosterone gel had significantly increased vascular density compared with controls ($P < 0.001$), as well as decreased collagen deposition.[37] More recently, immunohistochemistry has shown a significant increase in the absolute number of preputial blood vessels and vascular volume density, indicating PHT stimulates angiogenesis.[14] A further study has confirmed a significant increase in proliferating blood vessels and lymphocytic infiltrates 3 months following PHT.[21]

Impact on Hypospadias Surgery Outcomes

The effect of androgen-mediated inhibition of cutaneous wound healing is well documented. In mice, castration results in a striking acceleration of healing and a reduced inflammatory response,[38] and the androgenic pro-inflammatory effect prolongs urethral healing in rats.[39] In iatrogenic hypospadiac rabbits, post-operative testosterone-induced an exaggerated inflammatory tissue response compared with controls.[40] Moreover, in mice, DHT retarded in vitro migration of epidermal keratinocytes, suggesting a primary inhibitory effect upon re-epithelialisation.[41] Murine tissue studies also suggest that endogenous androgens retard cutaneous wound healing through their effects on collagenolytic enzymes (metalloproteinases).[42] Conversely, endogenous oestrogens, broadly speaking, are identified as enhancers of cutaneous wound repair.[43]

There is wide variability in hypospadias surgery post-operative complication rates, with disparate effects of PHT on surgical outcomes (Table 3). Some studies have suggested higher rates of complications,[46,48] particularly dehiscence,[21,47] which may be related to increased post-operative oedema and inflammation, but others have demonstrated significantly lower rates of overall complications,[23,24] reoperation[9,16,20] and glanular dehiscence.[16,20] Randomised controlled trials have shown reduced rates of meatal stenosis,[16] sometimes reaching statistical significance.[24] Trials have shown reduced rates of urethrocutaneous fistula,[16] frequently reaching statistical significance[23,24] with results confirmed through meta-analysis of a subset of three pooled randomised controlled trials.[9]

When surveyed, surgeons have suggested PHT increases bleeding,[3] but this is inconsistent with several operative papers.[32,33] One study ceased PHT 5-weeks pre-operatively to reduce any theoretical risk of intra-operative bleeding. Though the hypothesis was not tested scientifically, the study reported no bleeding problems.[16]

One randomised trial suggested a significant improvement in parental penile perception scores measured 3-months post-operatively, following PHT for distal hypospadias.[20] Another study identified adult men who underwent hypospadias repair in childhood and demonstrated similar complication rates between those who received testosterone and controls (50% vs. 43% respectively, $P = 0.54$).[7]

Non-randomised studies need to be interpreted with caution.[49] PHT may have been administered at the discretion of the surgeon due to various case differences,[45,48] so treatment and control groups may fundamentally differ. Because PHT use is associated with high-degree hypospadias phenotypes, poor outcomes may be biased against PHT. Although null results in such studies may signify no inherent value in the treatment, alternatively significant benefit may be hidden by a more severe disease type in the treatment arm. Furthermore, results may be biased by criteria for treatment, or the specific surgical technique selected.[46]

Table 3 Studies on the effect of pre-operative hormonal therapy on surgical outcomes

Country (year)	Design	Patient group (*N*)	Exposure	Surgical technique	Follow-up interval	Outcome
France (2020)[44]	Double-blind RCT	Mid-shaft or more proximal division of spongiosum (241)	1% promestriene cream 2 months prior to surgery EG ($n = 119$) CG ($n = 122$)	Onlay urethroplasty (multi-centre)	1 year	Healing complications (16.4% vs. 14.9% controls, $P = 0.86$)
India (2018)[20]	RCT	Distal hypospadias (186)	2 mg/kg testosterone enanthate (IM) monthly ×3. EG ($n = 94$) – 78 'responders' – 17 'non-responders' CG ($n = 92$)	TIP repair (single surgeon)	1.5 years (median)	Comparing 'responders' (those with increase glans width > 2 mm) to control group: Total complications (18% vs. 28.3%, $P = 0.15$) *Re*-operations (11.5% vs. 23.9%, $P = 0.04$) Glans dehiscence (3.9% vs. 14.1%, $P = 0.02$) Mean parent PPPS (8.88 vs. 8.03, $P = 0.03$)
Netherlands (2018)[7]	Retrospective cohort study	Adult patients, previous primary hypospadias repair in childhood (121), 50% available for clinical follow-up Of these (60); 24 had hormone treatment, 36 did not	Either: – Topical 5% testosterone propionate BD for 2 weeks *or* – Testosterone isocaproate (IM) 25 mg weekly for 2–3 weeks	Multiple techniques for repair of distal and proximal hypospadias.	18.3 years (median)	No difference in complications with or without testosterone therapy (50% vs. 43%, $P = 0.54$). Mean independent surgeon PPPS (88% vs. 92%, $P = 0.6$)
India (2017)[21]	RCT	Distal hypospadias (94)	2 mg/kg testosterone enanthate (IM) monthly ×3. EG ($n = 49$) CG ($n = 45$)	Single-stage urethroplasty, predominantly TIP.	Minimum follow-up 18 months	No difference in rate of urethrocutaneous fistula ($P = 0.438$) however wound dehiscence was exclusively seen in the treatment group ($P = 0.01$)
USA (2016)[45]	Prospective case–control study	Primary hypospadias repairs, distal and proximal (159)	'Testosterone cream' – strength, frequency or timing not specified. EG ($n = 84$) CG ($n = 75$)	140 single-stage procedures, 19 two-stage procedures	7 months (median)	11% larger glans width following PHT when compared to non-matched controls ($P < 0.001$) but no difference in urethroplasty or glanular complications.
China (2015)[23]	RCT	Primary proximal hypospadias repair with microphallus – <2.5 SD* below normal (72)	Oral testosterone undecanoate 2 mg/kg/day for 3 months *or* until microphallus resolved EG ($n = 36$) CG ($n = 36$)	Transverse preputial island flap (Duckett technique) – by a single surgeon	21 and 26 months (median for each group)	Reduced rate of urethrocutaneous fistula (5.9% vs. 25%, $P < 0.05$), urethral stricture (0% vs. 8.3%, $P > 0.05$) and overall need for reoperation ($P < 0.05$) in the testosterone arm. No glanular dehiscence or meatal stenosis observed.

(*Continues*)

Table 3 (Continued)

Country (year)	Design	Patient group (*N*)	Exposure	Surgical technique	Follow-up interval	Outcome
Iran (2015)[24]	RCT	Midshaft or distal hypospadias with flat urethral plates (182)	2 mg/kg testosterone enanthate (IM) monthly for 2 months before surgery EG ($n = 91$) CG ($n = 91$)	TIP repair	24 months (range 3–60 months)	Overall complication rates lower among treatment group compared with controls (5.5% vs. 13.2%, $P = 0.03$) Comparing specific complications rates between the treatment and control groups: – Urethrocutaneous fistula (4.4% vs. 7.7%, $P = 0.02$) – Meatal stenosis (1.1% vs. 3.3%, $P = 0.03$) – Glanular dehiscence (0.0% vs. 1.1%, $P = 0.07$) – Urethral diverticulum (0.0% vs. 1.1%, $P = 0.07$)
USA(2014)[46]	Retrospective cohort study	Primary hypospadias repair – proximal and distal (893) (73 received testosterone)	Testosterone injection in those with small glans, or later if glans diameter < 15 mm (details not available in abstract)	TIP repair	Not specified	Mean pre-treatment glans diameter 12 mm, increasing to 16.5 mm, compared to 15.4 mm in those not receiving testosterone. Urethroplasty complications increased with testosterone treatment (34% vs. 11%, $P < 0.0001$)
France (2011)[47]	Non-randomised controlled trial	Severe hypospadias (division of corpus spongiosum behind midshaft + significant chordee) (126)	Either – β-hCG 1500 IU IM every other day for 12 days (×6 doses) – Systemic testosterone 100 mg/m^2 IM monthly, ×2–6 (number of injections Determined by clinical effect on penile length (until ≥ 35 mm) – Both β-hCG and systemic testosterone EG ($n = 30$) CG ($n = 96$)	Onlay urethroplasty	Follow-up range between 10 and 97 months (mean: 41; median 34)	No significant difference in healing complications between PHT patients and those not receiving hormonal treatment (30% vs. 17.7%, $P = 0.23$) No significant difference in fistula/dehiscence rates in patients receiving PHT >3 months vs. < 3 months before surgery (21.7% vs. 57%, $P = 0.15$)

(*Continues*)

Table 3 (Continued)

Country (year)	Design	Patient group (*N*)	Exposure	Surgical technique	Follow-up interval	Outcome
France (2009)[48]	Retrospective cohort study	Severe hypospadias (proximal division of corpus spongiosum and marked ventral hypoplasia) (184) (76 received hormonal stimulation)	Either – β-hCG 1500 IU every other day for 12 days; – Testosterone 100 mg/m^2 IM – Topical dihydrotestosterone once daily for 2 months	Three techniques (onlay, buccal mucosa, Koyanagi type 1)	Mean follow-up 24 months (range 1–105)	Patients who received PHT had significantly more complications (46.8%) than those who did not receive any stimulation (26.8%), in the onlay group (39.5% vs. 24.2%) and in the buccal mucosa group (70% vs. 43.7%) (*P* values not given).
Austria (2008)[16]	RCT	Primary hypospadias repair – proximal and distal (75)	EG: 2.5% DHT transdesrmal gel once daily for 3 months, ceasing 5 weeks pre-operatively (37) CG: Nil hormonal treatment (38)	TIP repair	1 year	Comparing rates of complications in PHT group versus controls: – Meatal stenosis (0% vs. 5%, $P < 0.05$) – Fistula (3% vs. 11%, $P > 0.05$) – Glanular dehiscence (0% vs. 8%, $P < 0.05$) – Scarring (5% vs. 42%, $P < 0.05$) – Reoperation (3% vs. 24%, $P < 0.05$)

β-hCG, beta-human chorionic gonadotropin; CG, control group; DHT, dihydrotestosterone; EG, exposure group; IM, intramuscular; PHT, pre-operative hormonal therapy; PPPS, Parents Penile Perception Score; SD, standard deviation; TIP, tubularized incised plate.

Endocrinological Considerations and Sequelae

Immediate effects

Although topical therapy is perceived to be more benign, as it may reduce systemic effects, studies comparing parenteral and topical absorption suggest otherwise.[33] Topically administered testosterone and DHT can still be absorbed through the skin to the systemic circulation due to the high steroid permeability of the thin scrotal skin, which allows for swift and dose-dependent serum changes.[50] When ointments or creams are used, parents (especially mothers) are requested to wear gloves during application to prevent any inadvertent absorption,[34,51,52] which can lead to virilisation of parents or other children.[53]

Intermediate effects

The commonest adverse effects of topical testosterone are pubic hair growth (85%) and genital skin darkening (74%). These are typically transitory, disappearing within 90 days,[22] as are other early local effects such as penile skin irritation/redness and acne.[16,17,28,30–32,34] Administration of topical oestrogen (which was trialled in boys for its purported accelerative skin healing and anti-inflammatory properties[22,44]) unsurprisingly resulted in lower rates of pubic hair and genital pigmentation (13% and 50%, respectively).[22] Increases in the size and visibility of pubic hair follicles around the penoscrotal junction were reported following hCG therapy, which may aid surgical repair of proximal hypospadias by guiding skin flap demarcation.[29]

Many reports note minimal to no intermediate period adverse systemic effects following systemic[26,27,32] or topical[34,54] testosterone preparations. Topical DHT was noted to mildly and transiently suppress the pituitary-gonadal axis, and decrease the high-density lipoprotein-cholesterol:total cholesterol ratio.[52] Other studies utilising oral testosterone noted no endocrine suppression.[23] Polycythaemia is typically associated with long-term testosterone use, and the effect of a short course of testosterone in infancy is not well reported. Emesis following hCG[29] has been reported. Gynaecomastia was observed in 2% of the patients administered topical oestrogen (1% promestriene cream) preoperatively.[44]

Long-term effects

The long-term effects of PHT are poorly studied which has meant some units are cautious when utilising this treatment modality.[55]

Penile length and testicular development. Rat studies suggest that exogenous testosterone injected early in life eventually results in significantly shorter penile lengths. This was consistently found in normal[56] and hypogonadotropic hypogonadal microphallic phenotypes.[15,57] However, data from human fetal phallic tissue[58] suggests these findings are not translatable to humans.[51] The effect of PHT on human androgen receptor density and function (which is generally lower in the prepuce of patients with congenital penile malformations) did not change with exposure to subcutaneous testosterone.[58,59] Long-term follow-up studies have confirmed normal adult stretched penile lengths following childhood hypospadias repair with PHT (both topical and IM preparations), when compared to nomograms.[7]

It is noteworthy that in children with isolated microphallus, catch-up growth at puberty occurs regardless of IM testosterone treatment.[60] Furthermore, the main physiological factor leading to penile growth throughout childhood (outside of mini-puberty and puberty) is not testosterone. Stretched penile length increases from 3.3 cm at 1 year of age to 4.9 cm immediately before the onset of puberty,[61] with growth hormone and other growth factors likely involved.[62]

Findings from animal studies of reduced testicular weight, reduced tubular diameter, and germ cell count[56] are concerning. Whether this adverse testicular development impacts long-term fertility remains unknown.[55]

Skeletal. Investigations regarding bone growth are reassuring. When bone age was checked 1 year following testosterone treatment (topical or IM) during infancy (by evaluating the ossification centres of hands and wrists), no alteration was observed.[17,23,27,30,32,34] Normal bone age has also been noted in a child receiving up to 32 mg/kg of testosterone IM, 1-year following treatment.[25] Infants exposed to topical oestrogen had no significant difference in bone age compared to controls.[44] Testosterone PHT (topical or IM) during childhood had no effects on eventual adult height when compared with controls (180.1 vs. 179.0 cm, $P = 0.47$).[7]

Transdermal dihydrotestosterone has been shown to increase levels of serum alkaline phosphatase (a sensitive indicator of bone proliferation) in children with microphallus, though bone age and height velocity have shown not to be significantly affected at 1-year follow-up.[34,52]

Neurobehavioral and developmental effects. There is correlational evidence to suggest that the level of endogenous testosterone seen in the early post-natal period (mini-puberty) exerts a lasting organisational effect on sex-related behaviour.[63] However, no studies of hypospadiac patients receiving PHT have rigorously measured neurobehavioral or developmental outcomes; therefore, the status of PHT's neurobehavioral effects remains unknown.

Limitations

Studies are significantly heterogeneous primarily due to the inherently wide spectrum of hypospadias aetiologies and phenotypes. The aetiology of hypospadias is multifactorial and variations in androgen receptor density and function, 5-alpha reductase activity, and testicular steroidogenesis may all impact the efficacy of the various agents. Variations in the agent used, route of administration, dosage and timing of treatment will further impact results, as will various surgical approaches and perioperative management options (including dressings, catheterisation, antibiotics and duration).

The lack of consistent outcome definitions (e.g. meatal stenosis) and generally inadequate follow-up periods continue to consign the potential long-term effects of PHT to the unknown. Indeed, meaningful assessment of hypospadias surgery sequelae (psychological and physical) cannot be achieved unless patients are followed to maturity.[64] There is currently insufficient robust

evidence to allow a clinical guideline or recommendation to be constructed.

Conclusion

The use of PHT is non-uniform in reported clinical practice, and expert consensus remains elusive.[65] The need for a well-powered multi-centre prospective RCT to address this question is evident but unified agreement is required on: hypospadias severity classification; evaluation criteria and the place of biological screening; significant prognostic variables; application of surgical techniques; and outcome measures. Nonetheless, PHT has clear effects on penile morphometry, and more recent controlled trials suggest improved surgical outcomes. Possible indications for treatment include: proximal hypospadias, microphallus and prior to reoperations.[11] PHT may be used to improve outcomes in proximal and severe hypospadias, which represent a significant surgical challenge under the current paradigm.

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