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Biometry of the hypospadic penis after hormone therapy (testosterone and estrogen): A randomized, double-blind controlled trial

Kelly Christina de Castro Paiva [a,b], André Netto Bastos [g], Laura Pimenta Miana [c], Eveline de Souza Barros [c], Plínio Santos Ramos [d], Lara Meneguelli Miranda [e], Natália Maia Faria [e], André Avarese de Figueiredo [e], José de Bessa Jr [f], José Murillo B. Netto [c,e]

[a]Division of Pediatric Surgery, Department of Pediatrics, Federal University of Juiz de Fora (UFJF), MG, Brazil

[b]Division of Pediatric Surgery, Department of Pediatrics, Hospital and Maternidade Therezinha de Jesus of School of Medical Sciences and Health of Juiz de Fora (HMTJ/SUPREMA), MG, Brazil

[c]Division of Urology, Department of Surgery, Hospital and Maternidade Therezinha de Jesus of School of Medical Sciences and Health of Juiz de Fora (HMTJ/SUPREMA), MG, Brazil

[d]School of Medical Sciences and Health of Juiz de Fora (HMTJ/SUPREMA), MG, Brazil

[e]Division of Urology, Department of Surgery, Federal University of Juiz de Fora (UFJF), MG, Brazil

[f]Division of Urology, Department of Surgery, State University of Feira de Santana (UEFS), BA, Brazil

[g]Department of Morphology, Federal University of Juiz de Fora (UFJF), MG, Brazil

Correspondence to: José Murillo B. Netto, Av. Rio Branco, 2985/sl. 605, Juiz de Fora, MG, Brazil

andre@cortesvillela.com.br (A.N. Bastos)
jose.murillo@ufjf.edu.br (J.M.B. Netto)

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Summary

Introduction
The use of preoperative hormonal stimulation before hypospadias surgery aims to increase penile size and achieve better surgical results; however, the rules are not clear in the literature. We evaluated the effects of topical testosterone and estrogen in the hypospadic penis regarding biometric measures, side effects, and serum hormonal levels. To our knowledge, this is the first study using estradiol prior to hypospadias surgery.

Patients and methods
Sixty-nine children with hypospadias were randomly divided into three study groups: a control group (CG) of 17 children given placebo cream; a testosterone group (TG) of 28 children who used 1% testosterone propionate; and an estradiol group (EG) of 24 children using 0.01% estradiol. All subjects applied the topical ointment on the entire penis, twice daily for 30 days before surgical correction. Biometric evaluation of the penis included penile length and diameter, glans diameter, distance from the urethral meatus to the tip, and the width of the urethral plate. These measurements as well as serum hormone level, and side effects were evaluated prior to hormone use, and 30 and 90 days after.

Results
After 30 days an increase in penile diameter and length and diameter of the glans were observed in TG ($p < 0.05$). The width of the urethral plate and distance from meatus to the tip increased in TG, although not significantly. The most frequent side effects were appearance of pubic hair and darkening of the genital skin, mainly in TG, but these were transient and disappeared after 90 days of treatment. No significant variations were seen in serum hormonal levels (Table).

Conclusion
As in previous studies, an increase in penile length and diameter, and glans diameter was observed with the use of testosterone. Proximal urethral plate width and distance from the meatus to the tip of the penis had a tendency to increase also in TG. Estradiol did not change biometric measure of the penis. Few side effects occurred after both hormones, and any that did improved after 90 days follow-up and did not change hormone serum levels.

Conclusion
Preoperative use of topical testosterone increases penile size, diameter of the penis and glans. The use of estradiol does not change penile biometry. Side effects occur mainly with the use of testosterone and are transient. No significant and persistent hormonal changes were observed.

Table Positive finding of the study.

	CG	TG	EG	*p*-value
Variation in size in cm (median)				
Penile length	0.00 (0.0–0.0)	0.70 (0.2–1.4)	0.00 (0.0–0.4)	0.0005
Penile diameter	0.00 (0.0–0.1)	0.80 (0.0–0.3)	0.00 (0.0–0.0)	0.0094
Glans diameter	0.00 (0.0–0.1)	0.10 (0.0–0.4)	0.00 (0.0–0.1)	0.0026
Side effects, *n* (%)				
Pubic hair	0 (0%)	24 (85%)	3 (14%)	<0.0001
Darkening of skin	0 (0%)	21 (74%)	12 (50%)	<0.0001

Median (interquartile range).

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Introduction

Hypospadias is a congenital malformation characterized by an alteration in the development of the urethra, the ventral portion of the penis, and the prepuce, resulting in a wide range of locations of the anomalous meatus. It may be associated, in most cases, with a ventral penile curvature [1—3].

Surgical correction is recommended to ensure a better functional and an esthetic penis. Androgen stimulation has been used to increase penile size and improve surgical results, and its typical indications are children with small glans and in more complicated cases, such as proximal or cripple hypospadias [2—12].

Several studies have shown an increase in penile size, glans circumference, and improvement in vascularization with the use of testosterone, dihydrotestosterone and human chorionic gonadotropin [4—11]. However, the majority of studies are not well designed, not randomized, and without a control group [5,6,7,9,13,15,16].

The effects of estrogen on hypospadias surgery have not yet been demonstrated. Estrogen, as well as androgen receptors, has been found in the glans and prepuce of children with hypospadias [17]. It is known that estrogen acts against skin aging as it prevents decline of collagen fibers [18], increases water retention, and improves the skin barrier function [19]. The use of topical estrogen accelerates healing, increases collagen deposition, and reduces inflammatory cell influx [20]. These effects mean that changes in skin elasticity that occur over the passage of time are minimized [18,19]. Ashcroft et al. demonstrated that topical estrogen accelerated and improved wound healing in men and older women [21].

The present study aims to evaluate and compare the effects of estrogen and testosterone on penile growth, identify any side effects, and determine whether these hormones lead to alterations in serum hormonal levels in boys with hypospadias.

Materials and methods

A randomized, double-blinded controlled study was conducted with the participation of 75 children with different degrees of hypospadias and age ranging from 6 months to 10 years. Children with other penile or genital abnormalities, previous genital surgery, and those who have used hormones or any other medication that may interfere with the hypothalamic—pituitary—testicular axis were not included in the study.

The study was approved by the research ethics committee of our institution and received the protocol number: 983.247, according to the norms of the Declaration of Helsinki. Caregivers who agreed to participate in this study signed a free and informed consent form.

Children were randomly divided into three groups, using the Research Randomizer Form v4.0 (http://www.randomizer.org) program, according to the type of hormone used: CG (control group), children who used placebo ointment; TG (testosterone group), children who used 1% testosterone propionate ointment; and EG (estradiol group), children who used 0.01% estradiol ointment.

Use of ointment was chosen based on our previous experience [10] and other studies in the literature, to provide the same route of administration for all the hormones used, reducing any application bias between the study groups and not requiring children in the control group to receive unnecessary injections. The ointments were prepared at the university pharmacy. Parents were asked to wear gloves to apply the ointment all over their child's penis. After randomization, parents were asked to apply the ointment throughout the dorsal and ventral surface of the penis twice a day for 30 days before surgery.

The children were evaluated at three different timepoints (Fig. 1):

T1 (before using the ointment) — penile measurement and blood sample collection;
T2 (30 days after beginning of treatment — day of surgery) — penile measurement, blood sample collection, and evaluation of side effects;
T3 (90 days after hormone use) — blood sample collection and evaluation of side effects.

The same researcher made the penile measurements using a stainless steel caliper and ruler. The measures were: 1) length of the flaccid penis under maximum traction; 2) diameter of the penis at its base; 3) diameter of the glans, just above the balanopreputial furrow without retraction of the foreskin; 4) width of the urethral plate, proximal and distal; 5) distance from the meatus to the tip of the glans (Fig. 2).

A blood sample was collected for evaluation of total testosterone and its fractions, estradiol, FSH, and LH.

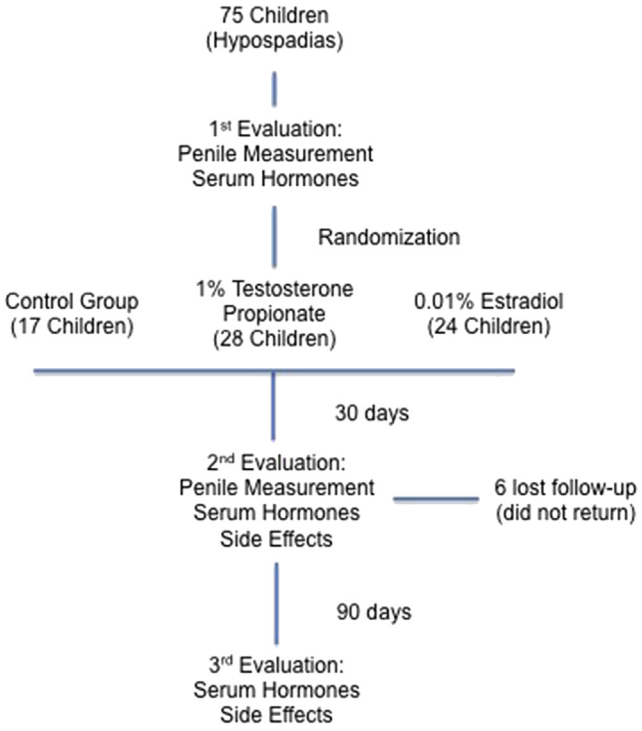

Figure 1 Study design.