Meta-analysis of Androgen Insensitivity in Preoperative Hormone Therapy in Hypospadias

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OBJECTIVE To define androgen insensitivity prevalence in hypospadias patients treated with preoperative hormone therapy.

MATERIALS AND METHODS We searched databases that were published in English and Chinese up to September 10, 2014 for our studies. Eligibility criteria were pre-established. Title, abstract, and full-text screenings were conducted by 2 authors independently. Discrepancies were resolved by consensus. Quality assessment of included studies was completed. Meta-analysis was done when appropriate using R, version 3.1.1 for Windows. Heterogeneity among individual studies was tested using the Cochran chi-square Q test and quantified by calculating the I^2 index.

RESULTS Thirteen of 1278 publications met inclusion criteria and were incorporated into this study. Of 306 patients with preoperative hormone therapy, 25 displayed androgen resistance. Meta-analysis demonstrated that the random-effects model generates a pooled estimate of 7.14% (95% confidence interval [CI], 3.16%-15.31%), whereas the fixed-effect model provides an estimate of 14.61% (95% CI, 10.00%-20.85%). Heterogeneity among included studies was found above medium ($I^2 = 67.1\%$ [95% CI, 41.2%-81.6%]; $P = .0003$]. After exclusion of the heterogeneity, both random-effects and fixed-effect models produce a consistent pooled estimate of 6.95% (95% CI, 0%-47.8%).

CONCLUSION We have defined that the prevalence of androgen resistance in hypospadias is 7.14% (95% CI, 3.16%-15.31%). To distinguish isolated hypospadias from patients with androgen insensitivity syndrome, we recommend that androgen-resistant patients should be specifically targeted by molecularly focused diagnosis. Management strategies should include identification of mutations in the androgen receptor gene, timely surgery to repair hypospadias, and long-term follow-up of sexual function and fertility later in life. UROLOGY 85: 1166–1172, 2015. © 2015 Elsevier Inc.

Androgen plays a central role in male external genital development. Androgen insensitivity syndrome is defined as a disorder that has complete or partial resistance to the biological actions of androgenic hormones in an XY man or boy who has normal testis determination and production of age-appropriate levels of androgenic hormones but has a function deficiency of androgen receptor.[1] The pathophysiological changes of this syndrome depend on the mechanism and effectiveness of androgenic hormones. Micropenis, severe hypospadias (perineoscrotal), and a bifid scrotum, although occur in various degrees, are typical clinical phenotypes of partial androgen insensitivity syndrome. A guidance on how to evaluate partial androgen insensitivity syndrome and other disorders of sex development for an infant or an adolescent has been established,[2] but definitive diagnosis relies on the identification of mutations in the androgen receptor gene that impede the normal function of androgenic hormones. A short course of testosterone (25 mg intramuscular injection monthly for 3 months) or topical dihydrotestosterone gel application would be able to determine the androgenic responsiveness.[3]

Hypospadias, defined as a malformation of the penis due to an incomplete development of the ventral part of the penis, is the second most common congenital anomaly in men, with a prevalence of about 4-6 in 1000 male births.[4] Although the etiology of hypospadias is still unclear, both genetic and environmental factors are implicated in the cause.[4] Hypospadias is generally an isolated disease and may also represent one of the clinical

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manifestations of androgen insensitivity syndrome. Reconstructive surgery is the main treatment of hypospadias when the patients are young and the penis is small. However, hypospadias repair is frequently associated with numerous complications including urethrocutaneous fistulas, meatal stenosis, urethral strictures, and scar formation.[5,6] To simplify the surgery and improve the surgical outcome, preoperative hormone therapy with testosterone, dihydrotestosterone, or human chorionic gonadotropin in hypospadias with small penises has been in some clinical practices for decades because it can temporarily compel phallic growth, which renders the surgical correction easier, reduces the non-negligible risk of complications, and improves the functional and cosmetic results after hypospadias repair.[7-14] However, preoperative hormone therapy has not been ubiquitously accepted and, in some extent, remained controversial.[15] Increasing concerns have been raised over potential negative effects of preoperative hormone therapy such as increased erections and pubic hair growth, and accelerated linear height and bone age.[7-9,16] In addition, androgens were reported to inhibit wound healing and increase inflammation.[17] A recent prospective, nonrandomized study implicated that hypospadias patients treated with preoperative testosterone might increase the risk of complications.[5]

Nevertheless, preoperative hormone therapy in hypospadias has generated significant benefits although some reports have brought up concerns for negative effects. Thus, it is imperative to increase the benefits and reduce the costs. It is well known that many hypospadias patients do not show response to preoperative hormone therapy as reported in numerous publications. However, the precise prevalence of androgen resistance in hypospadias is still obscure. Reliable estimates of the extent of androgen insensitivity will be essential for the development of clear and uniform approach to differential diagnosis and decrease of the costs. Therefore, we conducted a systemic review and meta-analysis of different individual studies to synthesize the results from individual studies and assess clinical androgen insensitivity prevalence in hypospadias patients treated with preoperative hormone therapy, aiming to provide reliable information for improving management strategies of the disease.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

We searched PubMed (from 1950 to September 10, 2014), EMBASE (from 1980 to September 10, 2014), and Chinese Biological Medicine (from 1978 to September 10, 2014) with the Medical Subject Heading terms "hypospadias" in combination with the additional term of "testosterone," "dihydrotestosterone," "chorionic gonadotropin," or "androgen insensitivity syndrome." In addition, the Cochrane library (http://www.cochrane.org) was searched with the terms of "hypospadias" and "testosterone." Furthermore, additional relevant literatures were reviewed from citations in the retrieved articles.

Inclusion criteria for our meta-analysis were predetermined as follows: (1) focus on human subjects, (2) hypospadias as primary diagnosis, (3) exposure of patients to some form of hormonal stimulation preoperatively, (4) performance of surgical repair, (5) summarizing the number of cases with no response to androgen stimulation, and (6) clinical research designation. Individual studies that did not meet the aforementioned criteria were excluded from this meta-analysis.

Data Extraction

Data were independently extracted by 2 investigators (W.Z. and J.Y.) and checked by other investigators for accuracy and quality. Discrepancies were resolved by consensus after discussions among investigators. Androgen insensitivity condition in hypospadias was identified as no response to preoperative hormone therapy. The related information was extracted from all included publications and summarized in Table 1. When data for a particular study were unclear or missing, we attempted to contact the authors. Unfortunately, in some cases, we were unable to obtain additional information.

Assessment of Study Quality

The quality of individual studies was assessed independently by 2 investigators (W.Z. and J.Y.) using the standard criteria adopted from the study by Jones et al,[18] modified to fit the objectives of this study (Appendix). The 8-point scoring system was based on factors that, we believed, would indicate the good quality of observational studies. Study design, case number, source of population, indication of hormone therapy, and reporting of nonresponse cases were included in our evaluation of the quality of included individual studies. Studies that received an overall score of $\geq$6 were classified as high-quality studies, those with an overall score of 3-5 were classified as medium-quality studies, and those with an overall score of $\leq$2 were considered as low-quality studies for the purpose of this analysis. These cut points were chosen according to the distribution of relative quality scores of all included studies. Disagreements were resolved through discussions with other investigators.

Statistical Analysis

Standard meta-analytic methods were used.[18] We compared the prevalence and variance in the random-effects model and in the fixed-effect model for aggregating individual effect sizes, aiming to have the reliable conservative estimate. Forest plots were generated showing the number of events, prevalence proportion for each of the included studies, and corresponding 95% confidence interval (95% CI) for each study. For pooled data, the I^2 index was calculated as a measure of the overall variation in prevalence that was attributable to between-study heterogeneity. Percentages of the I^2 index with $I^2 \leq 25\%$, $25\% < I^2 \leq 50\%$, $50\% < I^2 \leq 75\%$, or $I^2 \geq 75\%$ were interpreted as low, medium, above medium, and high heterogeneity, respectively. Publication bias was examined through the use of a funnel plot, and an asymmetry in the funnel plot was tested by using the Egger method.[19] All analyses were conducted using R, version 3.1.1 for Windows, and graphics were generated (R Core Team [2014]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/).

Table 1. Characteristics of included studies

Reference	No of NR	No of Cases	Penile Measurement	Hormone Used	Delivery Route	Hormone Dosage	Duration of Treatment	Karyotyping Abnormality	Patients Selected	Patient Age	Quality Score
Snodgrass et al[23]	13	28	GW ≥15 mm	T	IM	2 mg/kg 2-3×/mo	1 mo	2/9 cases	Middle, 5; proximal, 23	Mean, 10 mo	3
Ishii et al[20]	0	17	PL	T	IM	25 mg 1×/mo	3 mo	6/17 cases (no AR mutation)	Middle, 1; proximal, 16	1.4 ± 1.3 y (0-5 y)	4
Nerli et al[21]	4	21	PL and GC	T	Topical vs IM	2 mg/kg/wk 1×/d vs 2 mg/kg 1×/mo	3 wks vs 3 mo	N/S	Middle, 10; proximal, 11	Mean, 19 mo (16-27 mo)	3
Chalapathi et al[7]	1	25	PL	T	Topical vs IM	2×/d vs 2 mg/kg 1×/wk	3 wks	N/S	Distal, 4; middle, 12; proximal, 9	3.88 y (1-10 y)	4
Luo et al[13]	2	25	PL and GC	T	IM	25 mg 1×/mo	3 mo	N/S	Middle, 8; proximal, 16	9-12 mo	2
Li et al[25]	2	27	PL	T	Topical	2×/d	1 mo	0/13 cases	N/S	3-9 y	3
Koff and Jayanthi[12]	0	12	PL	HCG	IM	250 IU 2×/wk	5 wks	N/S	Middle, 7; proximal, 20	6-12 mo	1
Zhang and Sun[26]	2	35	PL	HCG	IM	1000 IU 2×/wk	5-7.5 wks	0	Middle, 23; proximal, 12	1-7 y	2
Wang et al[27]	1	18	PL	HCG	IM	500-1000 IU 1×/2-3 d	10-20 d	0	Proximal, 18	Mean, 4 y	3
Davits et al[8]	0	40	PL	T	IM	2 mg/kg 2× (first and fourth wks)	4 wks	N/S	N/S	Mean, 27.3 mo (13-74 mo)	3
Sakakibara et al[22]	0	15	Penile size	T	Topical	Cycle, 0.2-0.4 g 1×/d for 3 weeks in a mo	Average 3 cycles (1-10 cycles)	N/S	Middle, 4; proximal, 11	Mean, 4.1 y (2.9-9.5 y)	3
Gearhart and Jeffs[9]	0	36	PL	T	IM	2 mg/kg 2×/mo	1 mo	N/S	Distal, 4; middle, 23; proximal, 3	N/S	1
Tsur et al[24]	0	7	PL	T	Topical	2×/d	3 wks	1/7 cases (47, XYY)	Distal, 3; middle, 2; proximal, 2	Mean, 3.43 y (2-6 y)	3

AR, androgen receptor; GC, glans circumference; GW, glans width; HCG, human chorionic gonadotropin; IM, intramuscular; NR, nonresponder; N/S, nonspecified; PL, penile length; T, testosterone.

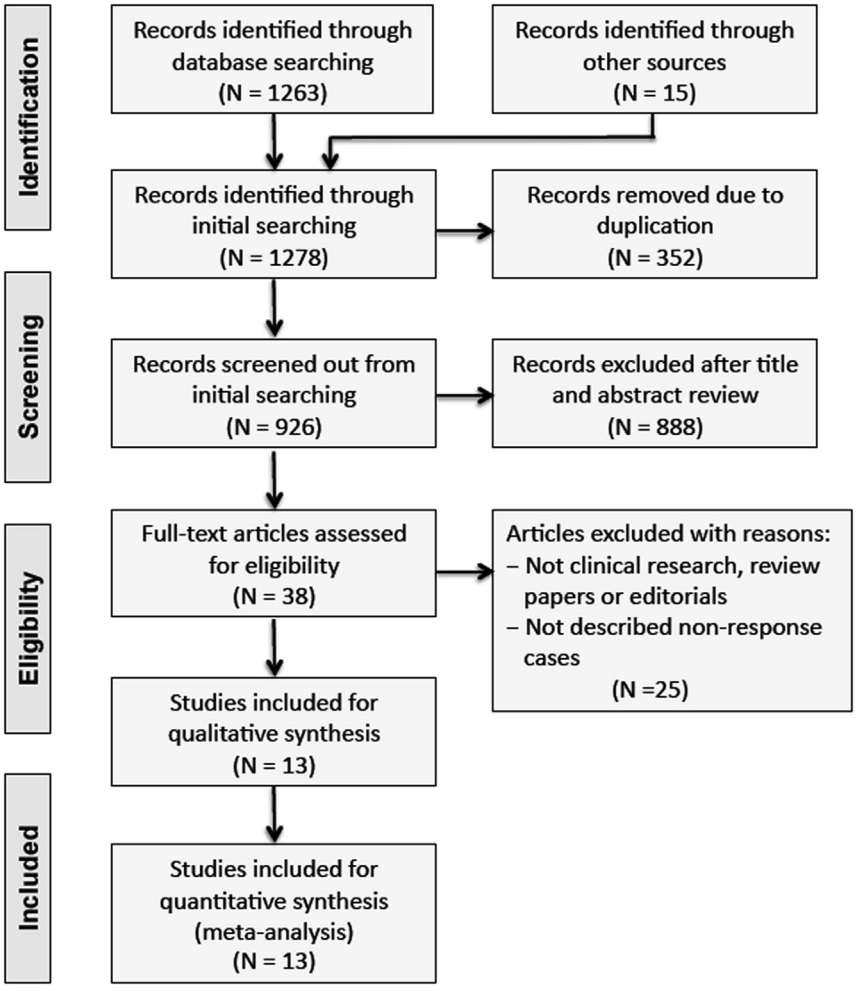

Figure 1. Flow diagram of literature search and individual studies identified for this systematic review and meta-analysis.

RESULTS

We initially identified 1278 potential relevant articles from our search of published literatures (Fig. 1). After removing duplicated records, we screened the remaining articles by title and abstract reviews and obtained 38 publications for further full-text investigations. Thirteen articles met all inclusion criteria, and their prevalence estimates were included in the overall meta-analysis.[7-9,12,13,20-27] The quality assessment of these individual studies based on the standard criteria (Appendix) showed that 69% (9 of 13) of these studies were of medium quality and 31% (4 of 13) were of low quality. Detailed descriptions of individual studies were summarized in Table 1.

These studies included 306 hypospadias patients treated with preoperative hormone therapy. Of 13 studies, almost half (6 of 13) had no androgen resistance, 2 had only 1 nonresponder, and 3 had only 2 nonresponders. Therefore, only 2 studies had >2 nonresponders. In fact, only 1 study provided 13 of the total 25 non-responders in this meta-analysis. Overall, 8.17% (25 of 306) of hypospadias patients treated with preoperative hormone therapy showed androgen resistance. The prevalence rates of androgen resistance in these 13 studies were ranged from 0% to 46%, with 95% CI from 0%-9% to 28%-66%.

Stringent overall prevalence was further investigated as a weighted average of individual summary statistics. The results were shown in the forest plot (Fig. 2). The random-effects model provided a pooled estimate of 7.14% (95% CI, 3.16%-15.31%), whereas the fixed-effect model produced a pooled estimate of 14.61% (95% CI, 10.00%-20.85%).

The forest plot showed that 12 of the 13 studies provided similar estimates, whereas the study by Snodgrass et al had a higher prevalence rate. Overall, heterogeneity among the individual studies was found above medium (I^2 = 67.1% [95% CI, 41.2%-81.6%]; P = .0003). However, after exclusion of the study by Snodgrass et al, homogeneity among the remaining 12 studies was observed (I^2 = 0% [95% CI, 0%-47.8%]; P = .6421). Further meta-analysis of these 12 studies showed that both pooled estimates generated in random-effects model and in fixed-effect model were 6.95% (95% CI, 0%-47.8%), consistent with those of the random-effects model (7.14% [95% CI, 3.16%-15.31%]) calculated from the analysis of all 13 studies, suggesting that the

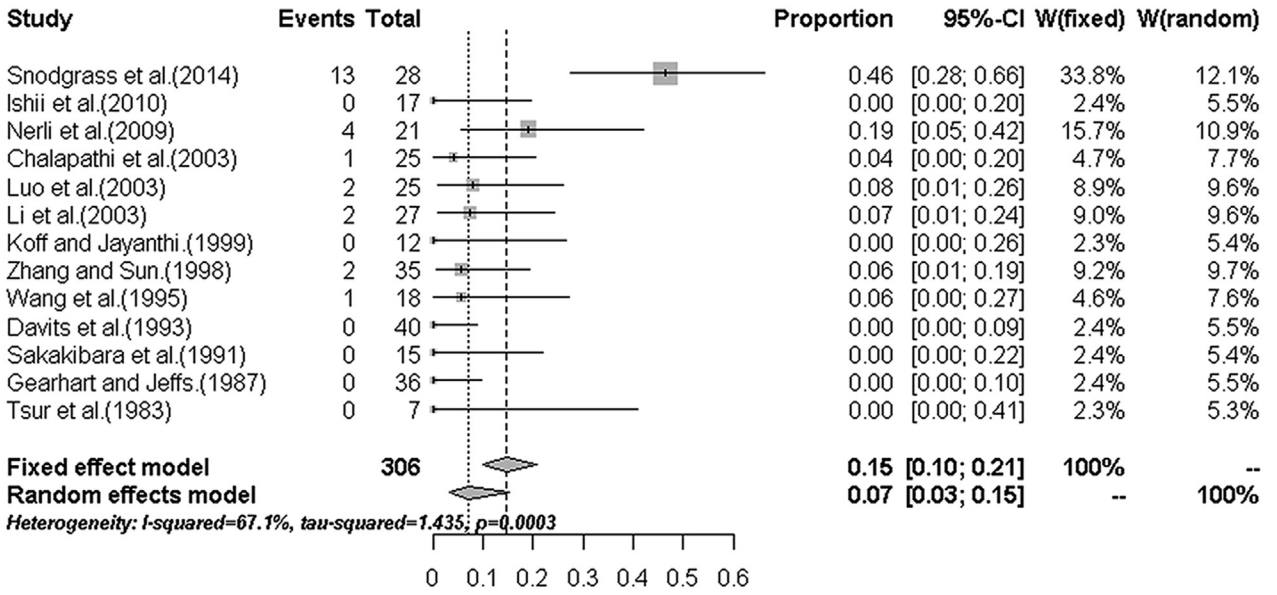

Figure 2. Prevalence of androgen resistance in hypospadias patients treated with preoperative hormone therapy. Forest plot shows number of events in total hypospadias cases and unadjusted prevalence estimate (square) with 95% confidence interval (bar) from individual studies. Weighted pooled prevalence estimates are represented as diamonds in this plot. CI, confidence interval.

overall prevalence from the random-effects model may be more accurate than that of the fixed-effect model.

The funnel plot for these studies showed an asymmetrical distribution of the individual studies (Fig. 3), indicating a publication bias. Statistical analysis of these data confirmed the high significance of publication bias (Egger test t value = −6.5039; degrees of freedom = 11; P = 4.404e-05).

COMMENT

Increasing number of studies reported androgen insensitivity after preoperative hormone therapy, but the precise extent of androgen resistance in hypospadias is obscure. Gearhart and Jeffs[9] described that 36.11% of hypospadias patients (13 of 36) did not have a significant increase in penile length or circumference after the initial testosterone injection (2 mg/kg). However, after 2 doses, phallic sizes of all patients were significantly increased. Ishii et al[20] showed that the effect of testosterone enanthate treatment on the penile length for hypospadias patients was significantly less than that for micropenis patients. Intriguingly, Snodgrass et al reported that as high as 66.52% (19 of 29) of patients with proximal hypospadias exhibited androgen resistance to certain extent.[23]

This review and meta-analysis aimed to synthesize the results from individual studies and define the frequency of androgen insensitivity in hypospadias patients who received hormone therapy preoperatively. Thirteen studies were screened out from 1278 publications based on predetermined criteria and showed weighted pooled estimates of 7.14% in the random-effects model and 14.61% in the fixed-effect model, respectively. About 2-fold difference of the pooled prevalence observed in the 2 models may result from the heterogeneity of overall variation in prevalence among all included studies as revealed by the I^2 index (67.1%; P = .0003) and the asymmetrical distribution of included individual studies in the funnel plot (t value = −6.5039; degrees of freedom = 11; P = 4.404e-05). Perhaps, the study by Snodgrass et al contributes to the heterogeneity as it had a much higher prevalence rate. The high proportion of proximal hypospadias patients (ie, 23 of 28) in the study is apparently associated with the high frequency of nonresponse or clinical androgen insensitivity (Table 1). Indeed, after exclusion of the study by Snodgrass et al that has an unusual estimate in the forest plot, the weighted pooled estimate of 6.95% was obtained from both models, consistent with the result in the random-effects model calculated from all 13 studies. Thus, it appears that all included 13 studies, even lack of sufficient homogeneity, are still comparable in the random-effects model that appears to provide an accurate and convincing pooled estimate in our meta-analysis.

Heterogeneity between individual studies suggests underlying important differences in study design, patient selection, hormone usage, dose regimens, routes of administration, sample sizes, and outcome report of the included eligible studies, all of which affect this meta-analysis. Given the lack of standardizations on penile or glans size for starting the therapy, drug selection, dose regimens, and routes of administration in included studies, it should be cautious to interpret the nonresponse patients in many of these reports. Nevertheless, our systematic review and meta-analysis is the first study to

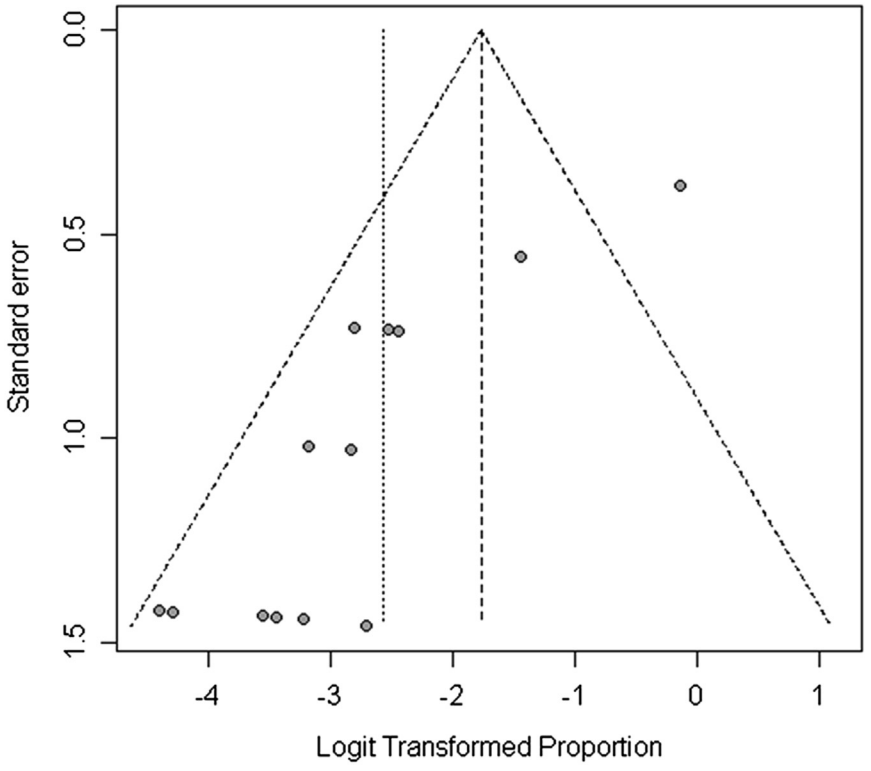

Figure 3. Funnel plot of included studies shows an asymmetrical distribution of the individual study and a publication bias (Egger test t value = −6.5039; degrees of freedom = 11; P = 4.404e-05).

provide precise prevalence of androgen insensitivity after preoperative hormone therapy.

To enhance the comparability across different individual study, we only used categorical approaches rather than dimensional approaches for our meta-analysis. Perhaps, further subdivision of patient groups, for example, distal hypospadias vs proximal hypospadias would be more informative. However, limited studies to date and limited sample sizes of the patients with preoperative hormone therapy in all included studies made it impossible to realize such more stringent evaluation. To enhance homogeneity of the samples, we were only able to include nonresponse patients in different individual studies, in which patients had different hypospadias classification and received different hormone treatment and might not equally respond to the therapy. It was reported that some patients did not response to testosterone at all at the initial step of the treatment but afterward exhibited much better response to testosterone.[9,23] We recommend that future studies on preoperative hormone therapy in hypospadias should establish standardized criteria, stratify patients based on hypospadias severity, include large sample sizes, and randomize controlled trials.

Considerable experience in patients with microphallus suggests that short-term courses (3 months) of testosterone in modest amounts (25 mg intramuscular injection every 4 weeks) were effective in promoting phallic growth but did not appear to have an adverse effect on skeletal growth.[3,28] Therefore, we recommend it as a standardized preoperative hormone therapy for hypospadias patients with microphallus in future studies. Penile length should be measured at least 4 weeks after the injections for elevating androgenic responsiveness. The recommended method for measuring penis is the stretched penile length. In boys with hypospadias, measurement of the dorsal aspect is the only way that can truly reflect potential penile length.[29] Nonresponse or clinical androgen insensitivity should be defined as no increase of penile size or penile length after the standardized preoperative hormone therapy.[23]

It should be noted that nonresponse to the preoperative hormone therapy in those hypospadias patients might partly be those patients with androgen insensitivity syndrome caused by the functional deficiency of androgen receptor. Care needs to be individualized, flexible, and holistic.[1] Management of androgen insensitivity patients should address molecular, functional, sexual, and psychological issues. Differential diagnosis of hypospadias patients with androgen resistance from those with androgen insensitivity syndrome would be important for the patient management. It was reported that 3% of (9 of 292) isolated hypospadias boys had androgen receptor missense mutations but did not show any phenotypic difference to the vast majority of hypospadias boys.[10] Some of such mutations may still retain their capacity to bind ligand and respond to the treatment with supraphysiological doses of androgen.[30] Clearly, identification

of the nature of mutations in the androgen receptor gene in all hypospadias patients will be important in differential diagnosis but will also significantly increase the costs. Our findings suggest that preoperative hormone therapy not only helps enlarge phallic size and consequently helps simplify the surgical procedure but also helps identify the patients with androgen insensitivity syndrome in a highly focused way. To maximize the benefits and minimize the costs in the hypospadias management, we propose that identification of androgen receptor mutations in hypospadias patients should specifically focus on those with androgen resistance instead of all hypospadias patients. Long-term follow-up of these patients is necessary to determine whether these mutations cause significant differences in sexual function and fertility later in life. Whether androgen insensitivity is an independent predictor of inferior outcome in hypospadias surgery needs further investigations.

CONCLUSION

In this study, we have revealed that the prevalence of androgen resistance in hypospadias patients is 7.14% (95% CI, 3.16%-15.31%). Considering the lack of response to hormone therapy may result from the patients with androgen insensitivity syndrome, we recommend that androgen resistant patients should be specifically targeted by molecularly focused diagnosis, and management strategies should include identification of mutations in the androgen receptor gene, timely surgery to repair hypospadias, and long-term follow-up of sexual function and fertility later in life. Randomized controlled trials, standardized dosing protocols, mutational analysis of the androgen receptor gene, and complete and consistent reporting should be considered in future studies to define the real accurate benefit of preoperative hormone therapy in hypospadias patients.

References

1. Hughes IA, Davies JD, Bunch TI, et al. Androgen insensitivity syndrome. *Lancet*. 2012;380:1419-1428.
2. Ahmed SF, Achermann JC, Arlt W, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. *Clin Endocrinol (Oxf)*. 2011;75:12-26.
3. Hughes IA. Early management and gender assignment in disorders of sexual differentiation. *Endocr Dev*. 2007;11:47-57.
4. Shih EM, Graham JM Jr. Review of genetic and environmental factors leading to hypospadias. *Eur J Med Genet*. 2014;57:453-463.
5. Gorduza DB, Gay CL, de Mattos ESE, et al. Does androgen stimulation prior to hypospadias surgery increase the rate of healing complications? A preliminary report. *J Pediatr Urol*. 2011;7:158-161.
6. Netto JM, Ferrarez CE, Schindler Leal AA, et al. Hormone therapy in hypospadias surgery: a systematic review. *J Pediatr Urol*. 2013;9:971-979.
7. Chalapathi G, Rao KL, Chowdhary SK, et al. Testosterone therapy in microphallic hypospadias: topical or parenteral? *J Pediatr Surg*. 2003;38:221-223.
8. Davits RJ, van den Aker ES, Scholtmeijer RJ, et al. Effect of parenteral testosterone therapy on penile development in boys with hypospadias. *Br J Urol*. 1993;71:593-595.
9. Gearhart JP, Jeffs RD. The use of parenteral testosterone therapy in genital reconstructive surgery. *J Urol*. 1987;138:1077-1078.
10. Kalfa N, Philibert P, Werner R, et al. Minor hypospadias: the "tip of the iceberg" of the partial androgen insensitivity syndrome. *PLoS One*. 2013;8:e61824.
11. Kaya C, Bektic J, Radmayr C, et al. The efficacy of dihydrotestosterone transdermal gel before primary hypospadias surgery: a prospective, controlled, randomized study. *J Urol*. 2008;179:684-688.
12. Koff SA, Jayanthi VR. Preoperative treatment with human chorionic gonadotropin in infancy decreases the severity of proximal hypospadias and chordee. *J Urol*. 1999;162:1435-1439.
13. Luo CC, Lin JN, Chiu CH, et al. Use of parenteral testosterone prior to hypospadias surgery. *Pediatr Surg Int*. 2003;19:82-84.
14. Monfort G, Lucas C. Dihydrotestosterone penile stimulation in hypospadias surgery. *Eur Urol*. 1982;8:201-203.
15. Malik RD, Liu DB. Survey of pediatric urologists on the preoperative use of testosterone in the surgical correction of hypospadias. *J Pediatr Urol*. 2014;10:840-843.
16. Wright I, Cole E, Farrokhyar F, et al. Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: a systematic review. *J Urol*. 2013;190:652-659.
17. Gilliver SC, Ruckshanthi JP, Hardman MJ, et al. 5alpha-dihydrotestosterone (DHT) retards wound closure by inhibiting re-epithelialization. *J Pathol*. 2009;217:73-82.
18. Jones L, Bellis MA, Wood S, et al. Prevalence and risk of violence against children with disabilities: a systematic review and meta-analysis of observational studies. *Lancet*. 2012;380:899-907.
19. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323:101-105.
20. Ishii T, Hayashi M, Suwanai A, et al. The effect of intramuscular testosterone enanthate treatment on stretched penile length in prepubertal boys with hypospadias. *Urology*. 2010;76:97-100.
21. Nerli RB, Koura A, Prabha V, et al. Comparison of topical versus parenteral testosterone in children with microphallic hypospadias. *Pediatr Surg Int*. 2009;25:57-59.
22. Sakakibara N, Nonomura K, Koyanagi T, et al. Use of testosterone ointment before hypospadias repair. *Urol Int*. 1991;47:40-43.
23. Snodgrass WT, Villanueva C, Granberg C, et al. Objective use of testosterone reveals androgen insensitivity in patients with proximal hypospadias. *J Pediatr Urol*. 2014;10:118-122.
24. Tsur H, Shafir R, Shachar J, et al. Microphallic hypospadias: testosterone therapy prior to surgical repair. *Br J Plast Surg*. 1983;36:398-400.
25. Li X, Wei G, Lin T, He D. External use of androgen in treating hypospadias with hypoplasia of penis in infants. *Chin J Pract Pediatr*. 2003;1:30-31; In Chinese.
26. Zhang F, Sun W. Use of chorionic gonadotropin in microphallic hypospadias. *Tianjin Pharm*. 1998;10:52-53; In Chinese.
27. Wang G, Chen S, Jiang X. Endocrine studies and treatment in patients with microphallic hypospadias. *Chin J Pediatr Surg*. 1995;16:23-24; In Chinese.
28. Grino PB, Isidro-Gutierrez RF, Griffin JE, et al. Androgen resistance associated with a qualitative abnormality of the androgen receptor and responsive to high dose androgen therapy. *J Clin Endocrinol Metab*. 1989;68:578-584.
29. Fievet L, Harper L, Chirpaz E, et al. Penile length is comparable in boys with and without hypospadias. *J Pediatr Urol*. 2012;8:493-496.
30. McPhaul MJ. Androgen receptor mutations and androgen insensitivity. *Mol Cell Endocrinol*. 2002;198:61-67.

APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2015.01.035.

Appendix. *Criteria for assessment of quality (maximum score = 8)**

1. Are the study design and sampling method appropriate for the research question? Random sample or whole population (1 point).
2. Is the sampling frame appropriate? Unbiased sampling frame (1 point).
3. Is the sample size adequate? Sample size greater than 100 individuals (1 point).
4. Are objective, suitable, and standard criteria used for administration of preoperative hormone therapy? Official records or self-report with appropriate questions (1 point).
5. Are objective, suitable, and standard criteria used for measurement of penile size? (1 point).
6. Are cases of non-response reported? Non-responders described (1 point).
7. Are the estimates of prevalence given with confidence intervals (CIs)? CIs reported (1 point).
8. Are the study subjects and the setting described in detail? Study subjects described (1 point).

*Assessment instrument was adopted from Jones et al (2012) and modified to fit the objectives of this study.