

Hormonal profile in children with isolated hypospadias associates better with comprehensive score of local anatomical factors as compared to meatal location or degree of chordee

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ABSTRACT

Background: To evaluate if hormonal profile of children with isolated hypospadias (IH) associates better with comprehensive local anatomical factor score (LAFS) than with clinically adjudged urethral meatus location or severity of chordee/k.j. **Material and Methods:** Ninety-nine children with IH were enrolled, as per inclusion criteria. Meatal location was recorded at first clinical examination in OPD; while LAFS was computed per-operatively using indigenously devised scale, except for neonates. Hypospadiacs were first classified into three standard meatal based groups and subsequently into LAFS based two groups (≤ 19 , >19). For all participants, pre HCG and post HCG (96 hour post- injection) estimation of serum gonadotropins, DHEA-S, estrogen (E), progesterone (P), testosterone (T) and Dihydrotestosterone (DHT) was done. Statistical tests were applied to assess significance of hormonal levels with respect to meatal location, chordee and LAFS. **Results:** Only FSH levels differed significantly among meatal based groups; while among LAFS groups, multiple hormonal differences were noted; with poor LAFS associated significantly with higher FSH, LH and lower E, T/DHT. Children with severe degree of chordee had poorer T output and a significantly lower LAFS as compared to those with moderate/mild chordee. **Conclusion:** Serotoli cell dysfunction, indirectly indicated by high FSH was found among midpenile hypospadiacs and those with poorer LAFS. Since groups based on LAFS revealed multiple intergroup hormonal differences than what was seen for meatal/chordee based groups; LAFS should be considered a better guide for prognostication and for deciding about hormonal supplementation. Lower androgenic output was particularly noted in children with severe chordee.

Key words: Children, human chorionic gonadotropin, hormones, hypospadias, local anatomical factor

INTRODUCTION

Hypospadias is a heterogeneous anomaly with varied presentation. It may be isolated or associated with other

anomalies; it may be mild or severe variant. The anatomical factors in hypospadiac patients not only affect the final repair technique but also influence the outcome following repair.^[1,2] Few, earlier studies have calculated hormonal profile in children with hypospadias but no study was particularly focused on evaluating the relationship of endocrinological profile of hypospadiac children with local anatomical features in these children.^[3-5] While studying, the hormonal profile in children with isolated hypospadiac viz-a-viz the control group in our earlier study,^[6] we also tried to find if the anatomical factors in children with hypospadias had any relation with their hormonal profile. Therefore, the same data was analyzed with a different

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perspective, by categorizing them on the basis of a comprehensive local anatomic factor score. This was to test the hypothesis that the severe variants of hypospadias (conventionally based on proximally located meatus) are more likely to bear the hormonal abnormalities that can lead to their poor outcome.

MATERIALS AND METHODS

Ninety nine (99) children (newborn to 12 years) with isolated hypospadias fresh cases attending pediatric Surgery OPD of our tertiary referral centre from May 2009 onwards were enrolled in this study, using strict exclusion criteria. They were otherwise healthy and had no associated anomalies also were not on any hormonal therapy. For all the participants, fasting morning blood samples were drawn between 8.30 to 9.30 a.m. (to take care of the diurnal variation of the hormonal levels) for estimation of serum levels of dehydroepiandrosterone sulfate (DHEA-S), Estrogen (E), Progesterone (P), Testosterone (T), Dihydrotestosterone (DHT), Luteinizing hormone (LH) and Follicular stimulating hormone (FSH). Thereafter, a single dose HCG (Human Chorionic Gonadotropin) stimulation test (to maximize hormonal output of testes) was given based on the recent National Health Service (NHS) protocol.^[7-9] Though; multiple HCG stimulation regimes are in vogue with comparable results and we employed the simplest one requiring a single intramuscular injection of HCG, to ensure good compliance.^[7,9] The study was cleared by the Institutional Ethical Committee and the hormonal assays were done at the Biochemistry laboratory of our institution.

The estimation of all above stated hormones except DHT was done using chemiluminescence method (Elycys 2010). The DHT estimation was done using ELISA as per the manufacture's instruction, DRG International Inc., USA. Testosterone levels were also estimated using ELISA too so that T/DHT could be computed. Pre and post HCG stimulation ratios for T were also calculated.

The age-wise subgroups with specific hormonal characteristics were identified: Neonates (n = 9), upto 4 year of age (n = 51), >4 to 8 year (n = 26) and >8 to 12 year (n = 13). The study subjects were initially classified as per the conventional classification based on clinically adjudged location of hypospadiac meatus i.e. proximal, mid or distal penile and mean \pm standard deviation for each of the assessed hormones was noted for the three groups. The subjects were again classified into two groups; this time based on local anatomical factors score (LAFS) which was usually per-operatively (at the time of undertaking first surgery for hypospadias repair), using indigenously

designed scoring method [Table 1], except for neonates in whom it was computed in outpatient department as surgery in them was to be performed later. The dividing lines used by us were based on the observations in our study subjects. The maximum score for each anatomic factor was '3' and was allotted to favorable or mild forms. Also, higher scores implied better anatomical factors. LAFS for each patient were tabulated; with range of 10 to 30 (mean being 20). We divided the study subjects in 2 categories (applying statistical software); those with score ≤ 19 (Gp I, severe variants) and other with > 19 (Gp II), as this division gave comparable number of subjects while keeping the dividing line close to the mean score. The third way to classify this data was on the degree of chordee and this was assessed per-operatively by measuring the angle between longitudinal axis of phallus and that of glans. The subjects were categorized as Gp 1 ($\leq 10^\circ$), Gp 2 ($>10^\circ$ - $\leq 30^\circ$) and Gp 3 ($>30^\circ$). The mean \pm SD for each hormone for each of above categories were computed. In all three grouping classes there was no statistical difference in the age-wise distribution of the subjects.

The entire data (i.e. hormone levels, hormonal ratios, subject categories) was managed on Excel sheet and was analyzed by using ANOVA 10.0. Hormonal differences between categories of study subjects (based on classification system used) were tested for significance using appropriate statistical tests. The two categories based on LAFS were compared for hormonal value using one way ANOVA, followed by *post hoc* Bonferroni method of adjustment in P values for multiple regressions. A $P < 0.05$ was considered significant.

Table 1: Local anatomical factors scoring system used in the study

Phallic length (objective) <3 cm=1, 3-4 cm=2, >4 cm=3
Phallic texture (subjective) flabby=1, mod developed=2, good texture=3
Urethral plate width at any point along its length (objective) <3 mm=1, 3-5 mm=2, >5 mm=3
Urethral plate texture (subjective) poor=1, moderately developed=2, good=3
Chordee measured after gitte's test ref before attempting its release and was recorded from the angle formed between the tangent drawn from maximum penile curve and the long axis of the phallus. (objective) severe $>30^\circ$ =1, moderate 10- 30° =2, mild 10° =3
Extent of urethral plate on glans (objective) 2mm proximal to tip=1, 1 mm proximal to tip=2, at tip=3
Glanular Texture (subjective) Dysplastic=1, moderate=2, good=3
Miscellaneous (objective) Hypogenitalia=1, penoscrotal transposition=2, hypopigmentation/lateral tilt=3
Preputial width—as measured from corona to outer extent of prepuce (objective)
<1 cm=1, 1-1.5 cm=2, >1.5 cm=3
Preputial frill circum—the widest distance measured between the points of preputial attachment to the glans (objective)
≤ 4 cm=1, 4-5 cm=2, >5 cm=3

RESULTS

Of 99 study subjects, 11 were clinically adjudged to have penoscrotal or proximal hypospadiac meatus (A); whereas 21 had mild penile (B) and 67 had distal penile, coronal or glanular meati (C), based on examination findings in outpatient department visit. On the other hand, based on LAFS, 50 subjects belonged to Gp I and 49 subjects belonged to Gp II. Based purely on the severity of chordee, the numbers of subjects were: 45 in Gp 1, 27 in Gp 2 and 27 in Gp3.

The mean LAFS of meatal based categories of hypospadias was compared using One Way analysis of Variance [Table 2]. Based on LAFS, it was observed that these groups differed from each other [Table 3]. All subjects with proximal hypospadias (Gp A) had LAFS ≤ 19 ; whereas, 67% of Gp B and 37% with Gp C subjects had low LAFS. On statistical analysis, we found that proximal penile hypospadias (Gp A) differed from the other two groups significantly; though distal and mid-penile hypospadiacs had no significant difference for LAFS.

When mean values of hormones were evaluated with respect to the meatal location and with severity of chordee [Tables 3 and 4], it was observed that the Gp B (midpenile hypospadiacs) had a significantly higher FSH in comparison to that of the other two groups. Also more severe chordee was associated with lower T levels in comparison to other two groups, though this difference was only marginally significant. Further it was noted that poor LAFS ≤ 19 was present in 85% children with severe chordee, 60% with moderate degree and 25% with minimal degree of chordee. Also, no subject with proximal (Gp A) hypospadias had minimal chordee; whereas, severe chordee was present in 28% of midpenile (Gp B) and 19% of those with distal (Gp C) hypospadiacs. This difference was found to be statistically significant.

When post hoc Bonferroni method of adjustment in P values for multiple regression was used for two categories of LAFS, it was noted that subjects in Gp I had higher LH (1.51 ± 2.42 vs 0.62 ± 1.99), FSH (1.60 ± 1.16 vs 1.13 ± 0.97) but lower E (6.12 ± 4.76 vs 10.01 ± 9.09) in comparison to those in Gp II [Table 5]. Gp II had a higher T/DHT (7.76 ± 8.00 vs 4.36 ± 4.71) (probably on account of lower DHT values in subjects with lower LAFS).

DISCUSSION

The key findings in children with isolated hypospadias in our study matched features with hypergonadotropic hypogonadism that was more pronounced in children

Table 2: Comparison of scores of individual anatomic factors in three groups of hypospadiacs based on meatal location

Variable	A (n=11) (proximal) %	B (n=21) (midpenile) %	C (n=67) % (distal)	Chi2	P value
P Length					
1	2 (18.18)	1 (4.76)	6 (8.96)	10.48	0.033
2	9 (81.82)	10 (47.62)	27 (40.30)		
3	0	10 (47.62)	34 (50.75)		
P texture					
1	2 (18.18)	4 (19.05)	5 (7.46)	14.46	0.006
2	6 (54.55)	11 (52.38)	16 (23.88)		
3	3 (27.27)	6 (28.57)	46 (68.66)		
U width					
1	7 (63.64)	7 (35.00)	33 (50.00)	NS	NS
2	3 (27.22)	10 (50)	19 (28.79)		
3	1 (9.09)	3 (15)	14 (21.21)		
U texture					
1	5 (45.45)	2 (9.52)	11 (16.67)	NS	NS
2	3 (27.27)	9 (42.86)	21 (31.82)		
3	3 (27.27)	10 (47.62)	34 (51.52)		
C degree					
1	8 (72.73)	6 (28.57)	13 (19.40)	16.89	0.002
2	3 (27.27)	7 (33.33)	17 (25.37)		
3	0 (00)	8 (38.10)	37 (55.22)		
Extent of Ur. Plate					
1	4 (36.36)	5 (23.81)	27 (40.30)	NS	NS
2	4 (36.36)	9 (42.86)	20 (29.85)		
3	3 (27.27)	7 (33.33)	20 (29.85)		
U texture					
1	3 (27.27)	2 (9.52)	2 (2.99)	9.95	0.041
2	4 (36.36)	8 (38.10)	21 (31.34)		
3	4 (36.36)	11 (52.38)	44 (65.67)		
Miscellaneous (in -ve range)					
1	7 (70.00)	11 (78.57)	38 (92.68)	14.92	0.021
2	0 (0.00)	1 (7.14)	2 (4.88)		
3a	2 (20.00)	0 (0.00)	0 (0.00)		
3b	1 (10.00)	2 (14.29)	1 (6.15)		
Pre. width					
1	2 (18.18)	3 (14.29)	13 (20)	NS	NS
2	9 (81.82)	13 (61.90)	36 (55.38)		
3	0 (0.00)	5 (23.81)	16 (24.62)		
Frill cir.					
1	3 (27.27)	5 (23.81)	16 (24.62)	NS	NS
2	8 (72.73)	14 (66.67)	36 (55.38)		
3	0 (0.00)	2 (9.52)	13 (20.00)		

* One way Anova followed by **Post hoc Bonferroni method of adjustment in P values for multiple comparison, P: Penile, U: Urethral, C: Chordee, Pre: Width, Preputial width, cir: circumference, NS: Non-significant

with more adverse anatomic factors that included more proximally located meatus, severe degree of chordee and dysplastic urethral plate/urethra over variable extents. The role of hormonal milieu, androgen receptors and multiple genes on formulation of male urethra has been well highlighted in the earlier studies.^[10-15] Few authors have studied hormonal profile in relation with meatal position. In a study, Boisen *et al.*, found that children with glanular hypospadias had a significantly higher FSH in comparison to healthy boys; whereas those with more severe degree of hypospadias had significantly different anthropometric

Table 3: Association of hormonal levels with meatal location

	Mean±SD			F value	P value	P value		
	A (n=11)	B (n=21)	C (n=67)			A vs. B	A vs. C	B vs. C
LAFS	15.36±2.5	18.85±2.8	19.71±3.0	10.82	0.0001	0.005	0.000	NS
FSH	1.13±0.61	1.97±1.56	1.22±0.91	4.30	0.01 (14.51)*	NS	NS	0.017

*One way Anova followed by **Post hoc Bonferroni method of adjustment in P values for multiple comparison, LAFS: Local anatomical factors score; FSH: Follicular stimulating hormone; NS: Non-significant

Table 4: Hormonal difference based on degree of chordee

Horm	Chordee degree based Groups			F value	P value	Chi2	1 vs. 2	1 vs. 3	2 vs. 3
	1 (n=47)	2 (n=21)	3 (n=21)						
LAFS	16.8±2.7	18.4±2.9	20.8±2.5	20.53	0.00	0.52	0.09	0.00	0.001
Testo 1 (peak)	3.17±1.4	3.9±2.11	4.45±2.32	2.98	0.056	6.62	NS	0.05	NS

*One way Anova followed by **Post hoc Anova Bonferroni correction for multiple comparisons, LAFS: Local anatomical factors score; Testo 1 (peak): Post HCG Testosterone; NS: Non-significant

Table 5: Relation of LAFS to hormonal levels

Hormone	Mean±SD		t value	P value
	1 (<=19) (n=50)	II (>19) (n=49)		
FSH	1.60±1.16	1.13±0.97	2.19	0.030
LH	1.51±2.42	0.62±1.99	1.98	0.049
E2	6.12±4.76	10.01±9.09	2.67	0.008
Progesterone	0.42±1.00	0.19±0.28	Ns	NS
Dheas	25.46±53.68	29.24±46.37	NS	Ns
Testo 0(c)	0.38±0.79	0.18±0.53	NS	NS
Testo 0(e)	0.78±1.06	0.57±0.80	NS	NS
Dht0	0.11±0.09	0.13±0.15	NS	NS
T0/DHT0(C)	3.81±8.24	1.06±1.79	2.28	0.024
T0/DHT0(E)	7.76±8.00	4.36±4.71	2.36	0.020
Testo 1(c)	2.04±1.21	2.66±1.70	NS	NS
Testo 1 (e)	3.80±1.93	4.11±2.26	NS	NS
Dht1	0.23±0.19	0.26±0.25	NS	NS
TI/Dht1(c)	12.19±9.39	13.77±9.65	NS	NS
TI/Dht1(e)	21.34±13.29	21.10±12.82	NS	NS
Dheas1	23.09±35.85	25.64±31.14	Ns	NS
Testo 1/testo0(c)	67.05±53.65	89.44±69.96	NS	NS
Testo 1/ testo0(e)	21.11±30.36	25.03±30.30	NS	NS

* and ** two way Student t-test: FSH: Follicular stimulating hormone mIU/ml; LH: Leutinizing Hormone mIU/ml; E2: Estrogen pg/ml; Progest.: Progesterone ng/ml; DHEAS0: Dehydroepiandrosterone (pre-HCG) ug/dl; Testo 0(c): Pre HCG Testosterone estimated by chemiluminescence assay ng/ml; Testo0(e): Pre HCG Testosterone estimated by ELISA ng/ml; DHT0: Dihydrotestosterone (pre-HCG) pg/ml; T0/DHT0(C): Pre HCG Ratio (Chemiluminescence); T0/DHT0(E): Pre HCG Ratio (ELISA); Testo 1(c): Post HCG Testosterone (Chemiluminescence) ng/ml; Testo 1 (e): Post HCG Testosterone estimated by ELISA ng/ml; DHT 1: Dihydrotestosterone (post-HCG) pg/ml; TI/DHT1(c): Post HCG Ratio (Chemiluminescence); TI/DHT1(e): Post HCG Ratio (ELISA); DHEAS1: Dehydroepiandrosterone (post-HCG) ug/dl; Testo 1/testo0(c): Post HCG testo rise (chemi); Testo 1/testo0(e): Post HCG testo rise (ELISA); NS: Non-significant

values in comparison to normal children.^[16] Holmes *et al.*, also observed a significantly higher levels of 17-OH progesterone and de-oxycortisol/11-OH deoxycortisol in subjects with distal hypospadias, with respect to the controls; but they did not assign much importance to this observation as levels of their precursor hormones were within normal limits.^[17] While Walsh *et al.*, found no

co-relation between meatal position and endocrinological profile.^[18] Fayert *et al.*, found lower anti-mullerian hormone (AMH) levels in two patients with proximal hypospadias. Though the latter did classify their patients on the basis of meatal position, they made no comparison of hormonal levels among these groups.^[19] There are other workers who found that the children with hypospadias have a lower testosterone output following HCG injection, but this was held to be true for only those with proximal hypospadias.^[3,13] In fact, Allen *et al.*, had excluded the subjects with lesser degree of hypospadias from their study aiming to analyze hormonal profile in children with hypospadias.^[13] Knorr *et al.*, also found subnormal testosterone response to HCG in 36 boys with hypospadias.^[4] Rey *et al.*, found testicular dysfunction in 57% of hypospadiac children which was more commonly associated in children with hypogonadotropic hypogonadism than with those with isolated hypospadias (14.8%).^[20]

In our study, a score for local anatomic factors was given in accordance with anatomical profile noticed in our study subjects. We uphold that these factors may vary with different population characteristics; but on reviewing the literature we found that the range of these normal values of the various factors (penile length, preputial width etc.) was not available for our study population and therefore, finding values beyond standard deviation from mean value could not be done. This could be considered as limitation of our study. However, as multiple factors were considered simultaneously, the net LAFS reflected a cumulative and buffering effect, while no single parameter predominated the score. This is unlike the more prevalent system of using either of meatal location or degree of chordee as the basis of classification. We noted a significant difference for penile length, spongiosal texture and degree of chordee, glanular texture and other associated anatomical factors between

proximal versus mid/distal hypospadias. The adverse LAFS was strongly associated with proximal variants, commensurating with observations of other authors.^[8] It is well observed that the surgical outcome is poorer in the patients with more severe variants of hypospadias (matching with poor LAFS in our study) and chances of post operation complications following corrective surgery are higher in these patients.^[1,2,21,22] Our method of LAFS scoring, was, however not validated and this can be considered as one of the limitations of our study.

Some workers found that supplementing testosterone in children with proximal/severe degree of hypospadias improves outcome of repair.^[23,24] whereas others feel that the same might be detrimental specially if androgens are given within 3 months of performing urethroplasty.^[24,25] Androgen injections are known to improve phallic length, vascularity and glanular texture.^[11] We opine that the nature of hormonal supplementation should depend on the nature of existing hormonal deficiencies in a given child. In our earlier publication noted no significant difference for the levels of androgens (T or DHT) within IH when three standard meatal based categories within the subjects with IH were compared.^[6] This observation can then question the rationale of supplementing androgens in subjects with IH. In our study the number of subjects in the three meatal based subgroups was far from being comparable and though it may appear to be a limitation of our study, our observation matches well with the known incidence of each of these subgroups (distal meatus location being the commonest) [Table 3]. In our current evaluation the only hormonal difference for meatal based categorization was a significantly higher FSH and that too, for mid penile hypospadiac group in comparison to the other two groups (proximal and distal). Higher FSH is known to be associated with spermatogenic failure and therefore this observation may point to the probability of serious future implications for this category of subjects.^[25-27] It is also worth mentioning that meatal based categorization in our study was based only on clinical examination, about one third of them would have qualified to be labeled as proximal hypospadiacs following orthoplasty had spongiosal divarication suggested by Barcats was used^[26,28] as severe degree of chordee was associated in as high as 28% of subjects with midpenile hypospadias. However, Barcat's method of classification has the limitation that it cannot be applied pre-operatively on the outpatient basis by majority of the practitioners who may be involved in management of children with hypospadias.

The significant difference of FSH as well as of anatomical score in these meatal based groups leads us to believe that these categories might have differing mechanisms

of genesis. It is important to note that Shima *et al.*, and Nonumura *et al.*, found a decreased post HCG androgenic output in patients with proximal hypospadias in comparison to milder variants.^[3,5] Though in our study, such a difference was not noted, a higher FSH value reflects that the gonad is 'not all too well' in the subjects with relatively proximally placed meatus and such patients require to be followed up carefully during adulthood. Also, it is further rational to postpone classifying a given case till per-operative assessment.

We also compared hormonal profile in subjects with unfavorable anatomic factors (independent of meatal location) with that in those with favorable factors (score >19). We found significantly higher gonadotropin output and a higher T/DHT ratio (largely due to lower DHT values as mean value of T levels was found to be slightly higher in low LAFS group) among those with lower scores. They, thus, fall into the category of hypergonadotropic hypogonadism.^[27] It will be a matter of debate if androgen supplementation (specially) can bring gonadotropins to normal levels in these children. Moreover, whether these children require DHT supplementation/that of testosterone as the mean values of the former is especially lower in those with adverse anatomic factors. However, as per guidelines of American Association of Clinical Endocrinologists (AAACE) testosterone supplementation should be good enough. Thus the treating surgeon may require supplementing hormones for optimizing short and long term results in children with low LAFS. It is further observed that androgenic replacement in hypergonadotropic hypogonadism not only causes full virilization among boys but also prevents osteoporosis, mood depression and even cardiovascular diseases.

One additional observation was significantly lower estrogen levels in those with poorer scores in comparison to those with higher scores. Experimental evidence suggests that estrogen plays an important role in spermatogenesis.^[29,30] Estrogen supplementation is known to improve wound healing as well.^[30,31] Does a low estrogen then reflect poor prognosis as regards wound healing and future spermatogenic functions in the subjects with poor anatomic profile? Only future longitudinal studies can answer this question. A few earlier studies have also highlighted that a few anatomic factors, specially the extent of urethral plate, can dictate the outcome following hypospadias repair.^[21,31,32] Perhaps the underlying pathogenesis might be related to the differences in the hormonal levels besides the anatomical factors, as were noted in our study. We also observed that in subjects with severe chordee except for lower levels of post HCG testosterone rise, no other hormonal differences were noted.

Our study has, however, highlighted a new aspect. When categories based either on the meatal location or the severity of chordee alone were considered with respect to the hormonal profile of isolated hypospadiacs, significant differences were noted for one hormone each. However, when the two categories formed on the basis of composite LAFS were compared, multiple significant hormonal differences were noted. We opine that the categorization based on LAFS is more rational as compared to the use of any single anatomic parameters (meatal location and severity of chordee) and this scoring system can even be applied on outpatient basis by the practitioners and pediatricians. The fact that multiple anatomic factor related hormonal differences were noted among hypospadiacs make us deduce that a disturbed hormonal milieu during critical period of embryogenesis has many more widespread adverse effects on the developing phallus apart from the more widely held disturbed urethral folds closure. It appears that varying severity of hormonal aberrations at that time-point gets manifested with corresponding severity of pathological anatomy among hypospadiacs. Though temporary hormonal supplementation may improve immediate surgical outcome, the long term fertility issues remain the matter of great concern in children with adverse anatomical factors

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