|| Print ISSN: 2589-7837 || Online ISSN: 2581-3935 ||
International Journal of Medical Science and Diagnosis Research (IJMSDR)
Available Online at www.ijmsdr.com
PubMed (National Library of Medicine ID: 101738825)
Volume 3, Issue 4; April: 2019; Page No. 37-45
Original Research Article
crossref DOI: https://dx.doi.org/10.32553/IJMSDR/v3i4.8

EVALUATION OF HYPOSPADIAS IN CHILDREN OF KOLKATA CITY, INDIA- AN OBSERVATIONAL HOSPITAL BASED STUDY

Dr. Rishavdeb Patra,[1] Dr. Sharmishtha Patra,[2*] Dr. Aneek Roychoudhary,[3] Dr. Aloke Sinhababu,[4] Dr. Sujitesh Saha,[5] Dr. Priyadershini Rangari[6]

[1]M.S., M.Ch., Associate Professor, Paediatric Surgery, [2*]M.S., M.R.C.O.G., Consultant Gynaecologist, Apollo Gleneagles Hospital,[3]D.N.B., M.CH., Senior Resident, [4]M.S., M.Ch., R.M.O., Clinical Tutor, [5]M.S., M.Ch., Associate Professor, [1,3,4,5]Institute Of Postgraduate Medical Education And Research, Kolkata, (West Bengal), [6]M.D.S., Assistant Professor, Department of Dentistry, Sri Shankaracharya Institute of Medical Sciences, Bhilai, Durg, Chhattisgarh.

Conflicts of Interest: Nil

Corresponding author: Dr. Sharmishtha Patra

Abstract:

Background: The incidence of developmental anomalies and disabilities associated with hypospadias is still a matter of controversy and data on this issue are sparse. Hypospadias is the second most common congenital anomaly in children. It is characterized by the abnormal ventral opening of the urethral meatus. Abnormal urethral opening may be located on the penile shaft, scrotum or perineum respectively.

Objective: The present study was aimed to study clinical profile of hypospadias cases at a super specialty hospital in Kolkata city.

Materials and Methods: We reviewed the records of 480 patients who underwent hypospadias repair from 2013 to 20018. Data collected for each patient included age, sex, demography, and major symptoms, duration of symptoms and relevant past and treatment history.

Results: In the present study of 480 patients were included in which the incidence was higher in 1-6 years of age. 256 patients were reported in 1-6 years of age i.e. in 53.32%. The various types of hypospadias were described in the study population, in which coronal and distal penile form were found to be more common i.e. in 55.62% subjects and glanular form found to be least incident i.e. 2.71% cases. 146 (30.41%) patients were associated with prepucial hood; 109 (22.7%), meatal stenosis; 98 (20.41%) patients were associated with severe chordee and 153 (31.87%) with narrow urethral plates. In case of distal hypospadias, 295 cases were detected and corrected. Glanular type was found to be least and distal hypospadias were with the highest incidence of 61.45%.

Conclusion: Posterior hypospadias was the most common anomaly in this study. It was associated with a high rate of extra abdominal wall anomalies, and physical and psychosocial disabilities. The significance of the latter findings with respect to the development of affected patients needs further clarification.

Keywords: Abnormal Urethral opening, Congenital anomalies, Genital anomalies, Hypospadias, Penile anomalies.

Introduction

Hypospadias is a congenital disorder of the urethra where the urinary opening is not at the usual location on the head of the penis. It is the second-most common birth abnormality of the male reproductive system, affecting about one of every 250 males at birth.[1,2]In roughly 90% of cases, the opening (meatus) is on or near the head of the penis (glans), referred to as distal penile

hypospadias, while the remainder have proximal penile hypospadias with a meatus near or within the scrotum. Shiny tissue seen extending from the meatus to the tip of the glans, which would have made the urinary channel, is referred to as the urethral plate.[3]

In most cases, the foreskin is also underdeveloped and does not wrap completely around the penis, leaving the underside of the glans penis uncovered. Also, a downward bending of the penis commonly referred to as chordee, may occur.[4] This is found in 10% of distal hypospadias[5] and 50% of proximal hypospadias[6] at the time of surgery. The scrotum may be higher than usual to either side of the penis, called penoscrotal transposition, adding to the abnormal overall appearance.

The abnormal urethral meatus may be located anywhere along the shaft to the perineum. The corpus spongiosum may be deficient or completely absent from the distal urethra. It occurs in 3.2 of 1000 live male births and can vary in severity from the glandular to the perineal position.1 Most often, it is the only abnormal finding, although in about 10% of cases, hypospadias may be part of a syndrome with multiple abnormalities.[7,8]

Fortunately the most distal varieties are both the most common and the simplest to correct. The anatomic findings vary in severity and are worst in cases in which the meatus is more proximally located. The hypospadias patients have an incomplete foreskin, called a dorsal hood because the foreskin is absent on the ventral surface of the penis. Frequently, the penis has ventral curvature called chordee due to fibrous tissue replacing the Buck's fascia which may vary in severity and location.[2]

Many congenital anomalies are noted at birth while others become apparent later in life during childhood or adolescence. Some malformations are incompatible with life; some can be corrected with surgery, while others though compatible with continued life but cannot be corrected with treatment. Some of the malformations are related to prematurity (e.g., patent ductus arteriosus), some to multiple births, and some to infertility itself.[10]

The most common associated defect is an undescended testes, which has been reported in around 3% of infants with distal hypospadias and 10% of those having proximal hypospadias.[9] The combination of hypospadias and an undescended testes sometimes indicates a disorder of sexual differentiation, and so additional testing may be recommended.[10,11] Otherwise no blood tests or X-rays are routinely needed in newborns with hypospadias.[3]

Hypospadias can be a symptom or indication of an intersex condition but the presence of hypospadias alone is not enough to classify as intersex. In most cases, hypospadias is not associated with any condition.[12]

Hypospadias is thus classified on the basis of anatomic localization such as glanular, penile, scrotal, perineal.[1,7]Genetic, endocrine and environmental factors are important in the aetiology of hypospadias.[3] It is classified into anterior (glandular and subcoronal), mid penile (distal penile, midshaft, and proximal penile), and posterior (penoscrotal, scrotal, and perineal) hypospadias.[5,6]

Hypospadias is thought to result from failure of the urinary channel to completely tubularise to the end of the penis; the cause is not known. Most often, it is the only abnormal finding, although in about 10% of cases, hypospadias may be part of a syndrome with multiple abnormalities.[7,8]

Hypospadias can be a symptom or indication of an intersex condition but the presence of hypospadias alone is not enough to classify as intersex. In most cases, hypospadias is not associated with any condition.[12]There is an increase in erectile problem in patients with hypospadias, particularly when associated with a chordee (down curving of the shaft). There is usually minimal interaction with ability to ejaculate in hypospadias providing the meatus remains distal. This can also be affected by the coexistence of posterior urethral valves. There is an increase in difficulties associated with ejaculation however including increased rate of pain on ejaculation and weak/dribbling ejaculation. Hypospadias is usually diagnosed in the newborn nursery by the characteristic appearance of the penis. The urinary opening ("meatus") is lower than normal, and most children have only partial development of the

foreskin, lacking the normal covering for the glans on the underside. The abnormal "hooded" foreskin calls attention to the condition. However, not all newborns with partial foreskin development have hypospadias, as some have a normal urinary opening with a hooded foreskin, which is called "chordee without hypospadias".[14,15]

Mega meatus with intact prepuce variant of hypospadias occurs when the foreskin is normal and the hypospadias is concealed. The condition is discovered during newborn circumcision or later in childhood when the foreskin begins to retract. A newborn with normal-appearing foreskin and a straight penis who is discovered to have hypospadias after a circumcision was started can have circumcision completed without worry for jeopardizing future hypospadias repair.[16,17] Hypospadias is almost never discovered after a circumcision.

The purpose of this study was to report prevalence of hypospadias and other associated congenital anomalies in children who were treated at a multispecialty hospital situated in Kolkata city.

MATERIAL AND METHODS

This was a hospital based observational study. Study was performed in the S.S.K.M. Hospital and Apollo Gleneagles Hospital, Kolkata; for a period of five years from July 2013 to June 2018. All patients with age greater than 12 months who underwent Hypospadias repair in the surgery department for five year of period were included in the study. 480 patients who were complained or previously diagnosed for hypospadias were considered for the study. Approval from Institutional ethical committee was taken before initiation of the study. Written informed consent was taken from all the parents of the study participants.

Patients with hemoglobin less than 9 gm%, patients having any other associated anomaly which required treatment on a priority basis and patients with proven or suspected intersex state were excluded from the study. Basic clinical examination was done for all the participants.

1. History and clinical examination

- Any structural and anatomical anomaly present at birth and any complications caused by the anomaly occurring over a period of time during study were assessed.
- Any symptoms and signs suggestive of visceral involvement were noted.
- Family history of similar complaints.
- All anomalies were registered and photographed at first and at follow up visits including with or without any intervention were noted.

2. Investigations

All patients were subjected to:

a) 2 D Echocardiography

b) Ultrasonography (USG whole abdomen)

Other Radiological investigations depending on clinical assessment site and type of birth defects.

Chest radiographs were supplemented by Contrast Enhanced Computed Tomography (CECT), Magnetic Resonance Imaging (MRI) with respect to their nature and extent and were repeated to assess the effect of the treatment modality employed if required.

Once the diagnosis of the type of anomaly is established during the course of clinico-radiological investigating process, the patient was subjected to one of the following mode of interventions, as per the type and status of the anomaly after optimizing the patient. The types of hypospadias have been classified into three according to the location of external urethral opening. As shown in images at last of this article.

• Proximal penile hypospadias-the opening of urethra located somewhere near the perineal or scrotal or peno-scrotal junction,

• Midshaft hypospadias-opening located along the shaft the penis,

• Distal Hypospadias-the opening of urethra located somewhere near or in the glans penis.

Data collected for each patient included age, sex, demography, and major symptoms, duration of symptoms and relevant past and treatment history. All patients underwent routine investigations as per anesthesia fitness, hemoglobin levels, urine routine and microbiological examination, renal function test, X-ray chest and USG- abdomen for associated anomalies screening.

The data collected was entered in a specially designed Performa and statistical analysis was

conducted using SPSS (16th version). Chi-square and t-test were performed to test the significance in bivariate. Descriptive as well as frequency distributions of all parameters were seen. Fisher extract test was used to analyze the data. A 'p' value of 0.05 was considered as statistically significant.

RESULTS

This study was conducted in a super specialty hospital situated at Kolkata city. The participants were the children aged more than 1 year of age, 480 subjects were tabulated. The data was taken from hospital registers for a longer duration of five years. All children having birth defect related to hypospadias were observed.

In the present study of 480 patients were included in which the incidence was higher in 1-6 years of age. 256 patients were reported 53.32% upto 6 years of age. Least number of patients found in >15 year age group i.e. 5.83% as shown in table 1. The mean age of presentation of patients of hypospadias was 7.55 years. Youngest one was 1 years of age and oldest was 22 years of age. The various types of Hypospadias were described in the study population, in which coronal and distal penile form were found to be more common i.e. in 55.62% subjects. And glanular form found to be least incident i.e. 2.71% cases.

In distal hypospadias type found with meatus at coronal 131 (27.5%) of patients and at distal penile 135 (28.12%) of patients as shown in Table 3. The least type found to be i.e. only 3 children showed the proximal perineal hypospadias.

In the present study of 480 patients, 146 (30.41%) patients of Hypospadias were associated with prepucial hood; 109 (22.7%), meatal stenosis; 98 (20.41%) patients were associated with severe chordee and 153 (31.87%) patients associated with narrow urethral plates as shown in the Table 3.

In case of distal hypospadias, 295 cases were detected and corrected. Glanular type was found to be in 13 patients (Table 1). These 80 cases were classified into proximal, midshaft and distal hypospadias. The most common among them were distal hypospadias with the incidence of 61.45%.

Associated birth defects are described in the Table 4. These birth defects were categorized depending upon anatomical origin into abdominal wall defects, urogenital defects, gastrointestinal (GIT) defects and some miscellaneous defects also observed. Abdominal wall birth defects were highest in all defects; in which inguinal hernia have 21.25%, omphalocele in 15.41% cases in males. Total incidence was 21.66% found in female children. The least occurred birth defects associated with Hypospadias were genitourinary tract defects in both genders.

Distal type of hypospadias was found to be most common type and glanular type was least common in the sand set of population as shown by the Table 2.

Table 1: Age distribution of study participants.

Age in years	No. of Patients	%
1 to 3	141	29.37
4 to 6	115	23.95
7 to 9	83	17.3
10 to 12	71	14.8
13 to 15	42	8.75
> 15	28	5.83
Total	480	100

Table 2: Type of Hypospadias among study participants.

Type of Hypospadias	Site of Urethral Opening	No. of Patients	%
Glanular	Glanular	13	2.71
Distal	Coronal	131	27.5
	Distal penile	135	28.12
	Midpenile	29	6.04
Proximal	Proximal penile	62	12.91
	Penoscrotal	105	21.87
	Perineal	3	0.55
Total		480	100

Table 3: Clinical findings among various types of Hypospadias.

Association	Glanular Hypospadias		Distal Hypospadias		Proximal Hypospadias	
	No of patients	%	No of patients	%	No of patients	%
Narrow urethral plate	13	2.70	68	14.16	72	15.62
Meatal stenosis	8	1.66	65	13.54	36	7.5
Severe Chordee	12	2.5	58	7.91	28	5.83
Prepucial hood	8	1.66	104	21.66	34	7.08
Total	31	6.45	295	61.45	170	35.41

Table 4: Systemwise distribution of Birth defects associated with Hypospadias.

System	Defect	N	%
Abdominal Wall	Inguinal Hernia	102	21.25
	Omphalocele	74	15.41
	Total	176	36.66
Genitourinary tract	MCDK	23	4.79
	Hypospadias	11	2.29
	PUJO	24	5.0
	Undescended Testes	12	2.5
	Vesico-ureteric reflux	18	3.75
	Total	88	18.33
GastrointestinalTract defect	Hirschsprung's disease	13	2.7
	Biliary atresia	10	2.08
	Enteric duplication cyst	11	2.29
	Tracheo Oesophageal fistula	07	1.45
	Total	41	8.54
Miscellaneous	Hemangioma	11	2.29
	Retinoblastoma	08	1.66
	Cleft lip	24	5.0
	Total	84	17.5

Table 5: Incidence of hypospadias in different population

Types of hypospadias	Proximal hypospadias	Midshaft hypospadias	Distal hypospadias
Duckett et al	30%	21%	49%
Wang-Hseng Wu et al	65.7%	9.6%	24.7%
Hadidi et al	15%	75%	10%
Orkiszewskiet al	10%	63.3%	26.7%
Patra et al	13.8%	78.6%	7.6%
Present Study	35.41%	3.14%	61.45%

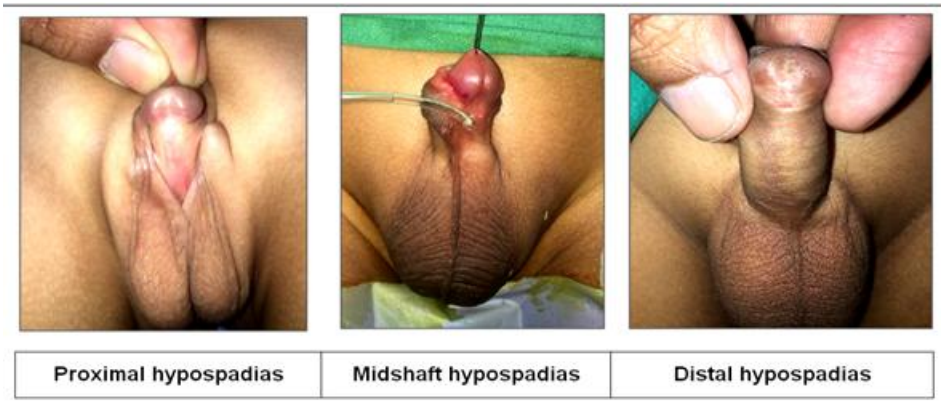

Figure 1: Types of Hypospadias

DISCUSSION

Hypospadias is one of the most common congenital defects affecting the external male genitalia.[18,19] The incidence is around 1 in 250 male newborns, although its incidence seems to be increasing. Hypospadias is defined as an insufficient development of the urethral fold and the ventral foreskin, with or without penile curvature.[20]

The urethral opening is located more proximally anywhere between the tip of the penis and the perineum. Hypospadias classification is based on the position of the meatus, within three categories: distal or anterior hypospadias with the meatus on the glans penis, at the corona, or subcoronal.[21]Mid-penile hypospadias with urethral opening located on the distal penile shaft, midshaft, or on the proximal penile shaft. Proximal or posterior hypospadias have a penoscrotal, scrotal, or perineal urethral meatus location. Distal hypospadias is the most common finding in the Western world. In Asia more, proximal forms are observed.[22]

Most commonly used classification of hypospadias relates to the location of the meatus however, the severity of hypospadias can't always be defined by original site of the meatus.[23] The solid mass of endodermal cells derived from urogenital sinus extends into the phallus called urethral plate. The urethral plate breaks down and forms the urethral groove. The edges called urethral folds fused with each other and convert into a tube called urethra. This fusion occurs caudal to cranial direction. Failure or alteration of fusion in urethral plate is called as hypospadias.[24] One of most accepted etiology of hypospadias may be due to androgen metabolism abnormalities or androgen receptors defects. 5α-reductase enzyme deficiency is one of the causes of hypospadias. Genetic syndromes such as hand foot genital syndrome, an extremely rare autosomaldominant disorder characterized by mutation in HOXA13. The environmental pollutants with substances enriched in estrogenic activity (insecticides, natural estrogens from plants and chemicals from plastic industry) are transmitted through food chain also possible

etiological factors for worldwide increase in incidence of hypospadias.[26,13]

Severity of hypospadias should be classified according to the new location after correction of chordee. The most accepted and simplest classification has been described by Kaufmann who classified hypospadias into first degree (Glanular), Second degree (Penile) and Third degree (Proximal).[33] Our study was based on similar classification.

In the present study of 480 patients, 29 (6.04%) patients of hypospadias having meatus at midpenile region in both groups and as compare to study of Quetta[10] where 49 (52%) patients of hypospadias having meatus at subcoronal/ distal penile region and 35 (37.4%) patients of hypospadias having meatus at midpenile/ proximal penile region. In the present study of 480 patients of hypospadias 53.33% patients were below 6 years of age and mean age of presentation is 7.55 years., as comparisonwith a study of 94 patients of hypospadias at BMC Hospital Quetta, 61% patients were below 5 years of age with mean age of presentation was 6.7 years and as comparison with a study of 304 patients of hypospadias at Asopa hospital Agra, 62.5% patients were below 5 years of age.[10]

This difference in late presentation for operative intervention is due to less awareness and seriousness for hypospadias in people coming from lower socioeconomic class mainly.

In the present study of 480 patients, 146 (30.41%) patients of Hypospadias were associated with prepucial hood, 109 (22.7%), meatal stenosis, 98 (20.41%) patients were associated with severe chordee and 153 (31.87%) patients associated with narrow urethral plates as shown in the Table 3.

In the present study, the most common type was distal hypospadias (61.45%) followed by incidence of proximal hypospadias (35.41%) and midshaft hypospadias (22.5%). The present study revealed a very high incidence of distal hypospadias (61.45%) which is similar to the findings reported by Gohil A et al.[24] 62.5% and Duckett et al who had recorded the incidence of distal hypospadias in 49% cases.[24] Very low incidence 7.6% and 10% was reported by Patra et al and Hadidi et al respectively.[39,41]

The incidence of midshaft hypospadias in our study was 3.14% which is not similar with the incidence reported by Duckett et al (21%).[37] But it was contradicting to Orkiszewski et al,[41] Hadidi et al[39] and Patra et al,[42] who reported the incidence was 63.3%, 75% and 78.6% respectively. This incidence was higher than the present study. Wang-Hsengwu et al did a similar study and reported a lower incidence of midshaft hypospadias (9.6%).[40]

The incidence of proximal hypospadias in the present study was 35.41%. Studies by Duckett et al[37] reported similar results i.e. 30%. Orkiszewski et al, Patra et al, and Hadidi et al recorded the lower values than our study i.e. 10%, 15% and 13.8% of cases respectively.[39,41,42] The higher incidence was reported by Wang-Hseng Wu et al (65.7%).[17] Incidence of hypospadias in different population has been explained in Table 5.

CONCLUSION

Most cases (70.62%) of hypospadias were presented at age 9 years and below. Most common type of hypospadias was distal and coronal followed by penoscrotal type. Hypospadias was associated with prepucial hood in 146 cases (30.41%), meatal stenosis was found in 109 subjects (22.7%), Chordee in 98 children (20.41%) and narrow urethral plates in 153 patients (31.87%) out of total cases.

We proposed the standard classification of hypospadias with the higher incidence was found to be in distal hypospadias. Associated birth defects were found to be highest in abdominal wall (36.66%) i.e. inguinal hernia in 102 cases (21.25%). The least common was undescended testes (2.5%).

The exact cause of hypospadias is not known. In the vast majority of cases, the condition is repairable, leaving a functional and normal looking penis. With modern technologies and techniques, hypospadias and chordee repair procedures are highly successful provided early diagnosis and treatment is done and with the right support, any emotional distress is avoidable.

REFERENCES

1. Ader, P.L. and Hobson, H.P. 1978. A review of the Veterinary literature and a report of three cases in the dog. J Am Anim Hosp Assoc., 14: 721–7.
2. Alam, M.R., Shin, S.H., Lee, H.B., Choi, I. H. and Kim, N.S. 2005. Hypospadias in three calves: a case report. Vet Med-Czech., 50 (11): 506–9.
3. Al-Ani, F.K., Khamas, W.A., Al-Qudah, K.M. and Al-Rawashdeh, O. 1998. Occurrence of congenital anomalies in Shami breed goats: 211 cases investigated in 19 herds. Small Rumin. Res., 28: 225-32.
4. Baskin, L.S., Himes, K. and Colborn, T. 2001. Hypospadias and endocrine disruption: is there a connection? Environ. Health Perspect., 109: 1175-83.
5. Baskin, L.S. 2002. Hypospadia and genital development symposium. Advances in experimental medicine and biology. Proceedings of the Hypospadias and genital development symposium. University of California, San Francisco.
6. Dennis, S.M. and Leipold, H.W. 1979. Ovine congenital defects. Vet. Bull., 49: 233-9.
7. Kahn, C. M., Line, S. and Aiello S. E. 2005. Urinary System. The Merck Veterinary Manual, 9th ed. Merck and Co. Inc., Whitehouse Station, N. J., USA, pp. 1249–1287.
8. Kim, K.S., Torres, C.R.Jr., Yucel S., Raimondo K., Cunha, G.R. and Baskin, L.S. 2004. Induction of hypospadias in a murine model by maternal exposure to synthetic oestrogens. Environ. Res., 94: 267-275.
9. Radostits, O.M., Gay, C.C., Hinchcliff, K.W. and Constable, P.D. 2007. Veterinary Medicine. 10th Edn., London, Saunders Co., pp. 573.
10. Sharma, S.N. and Singh.J. 1995. The Urinary System. In Ruminant Surgery, Eds. Tyagi, R. P. S. and Jit Singh. CBS Publishers, Delhi, India. pp. 272.
11. Sharpe, R. and Skakkebaek, N. 1993. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet., 341 (8857):1392-5.
12. Silver, R.I. 2000. What is the aetiology of hypospadias? A review of recent research. Del. Med. J., 72: 343-7.
13. Yamada, G.A., Satoh, Y.A., Baskin, L.S.B., Cunha, G.R.C. 2003. Cellular and molecular mechanisms of development of the external genitalia. Differentiation., 71(8): 445–60.
14. Duckett JW. Hypodadias. Campbell's text book of urology 7th ed. 1998:2093-119.
15. Devine CJ Jr & Horton CE. A one-stage hypospadias repair. .Journal of Urology. 1961; 85:166-72.
16. Ságodi L, Kiss A, Kiss-Tóth E, Barkai L. Prevalence and possible causes of hypospadias Orv Hetil 2014;155:978-85.
17. Bhat A. General considerations in hypospadias surgery. Indian J Urol. 2008; 24:188-94.
18. Khuri FJ, Hardy BE Churchill BM. Urologic anomalies associated with hypospadias. Urol Clin N Am 1981;8:565-71.
19. Kim SC, Kwon SK, Hong YP. Trends in the incidence of cryptorchidism and hypospadias of registry-based data in Korea: a comparison between industrialized areas of petrochemical estates and a non-industrialized area. Asian J Androl 2011; 13:715-8.
20. Hinman F Jr, Baskin LS. Hypospadias. In: Hinman's Atlas of Pediatric Urologic Surgery. 2nd ed. Philadelphia: Saunders Elsevier; 2008;653– 61,
21. Kraft KH, Shukla AR, Canning DA. Hypospadias. Urol Clin North Am. 2010;37:167-81.
22. Baskin LS, Ebbers MB. Hypospadias: anatomy, etiology, and technique. J Pediatr Surg 2006;41:463-72.
23. Ahmed J. Tranverse preputial island flap for Hypospadias repair. J.surgery Pak. 2010;15:139-43.
24. Gohil A, Nema A. A study of clinical profile of hypospadias cases at a medical college hospital of South Gujarat, India. Int Surg J 2018;5:2127-30.
25. Suresh NM, Kattepura S, Yathindra N, Afroze KH. Incidence of types of hypospadias in and around Tumkur district, Karnataka, India: an anatomical classification. Int J Res Med Sci 2018;6: 1161-4.

26. Baskin LS. Hypospadias, anatomy, embryology and reconstructive techniques. Braz J Urol. 2000; 26(6):621-9.

27. Djakovic N, Nyarangi-Dix J, Özturk A, Hohenfellner M. Hypospadias. Advances in Urology. 2008.

28. Sutherland RW, Wiener JS, Hicks JP, Marcelli M, Gonzales ET, Roth DR, Lamb DJ. Androgen receptor gene mutations are rarely associated with isolated penile hypospadias. J Urol. 1996; 156(2):828-31.

29. Holmes NM, Miller WL, Baskin LS. Lack of defects in androgen production in children with hypospadias. J Clin Endocrinol Metab. 2004; 89:2811-6.

30. Silver R, Russell D. 5alpha-Reducatase type 2 mutations are present in some boys with isolated hypospadias. J Urol. 1999; 162:1142-5.

31. Allegra A, Herbs MA, Griffin JE, Wilson JD, Schweikert HU, McPhaul MJ. Mutations of the androgen receptor coding sequence are infrequent in patients with isolated hypospadias. J Clin Endo Metab. 1995;80 (9):2697-9.

32. Singh I, Pal GP. Human embryology. 2014:264-69.

33. Kaufmann DC. Verletzungen und Krankheiten der männlichen Harnröhre und des Penis, von Dr. C. Kaufmann, F. Enke; 1886:18-39.

34. Smith CK. Surgical procedures for correction of hypospadias. J Urol. 1938;40:239.

35. Browne D. A comparison of the duplay and Denis Browne techniques for hypospadias operations. Surgery. 1953;34:787.

36. Schaefer AA, Erbes J. Hypospadias. Am J Surg. 1950;80(2):183-91.

37. Duckett JW. Hypospadias. In: Gillenwater JT, Grayhack JT, Howard SS, Duckett JW, editors. Adult and pediatric urology. 3rd Ed. St Louis: Mosby Year Book;1966: 2550-65.

38. Avellán L. Morphology of hypospadias. Scand J Plast Surg. 1980;14:239-47.

39. Hadidi A. Classification of hypospadias. In: Hadidi AT, Azmy AF, editors. Hypospadias Surgery, an illustrative guide. Berlin: Springer-Verlag;2004:79-82.

40. Wu WH, Chuang JH, Ting YC, Lee SY, Hsieh CS. Developmental anomalies and disabilities associated with hypospadias. J Urol. 2002;168(1):229-32.

41. Orkiszewski M. A standardized classification of hypospadias. J Pediat Urol. 2012;8(4):410-4.

42. Patra SS, Swain NN. The study of spectrum of hypospadias and evaluation of its associated anomalies in eastern parts of India. J Evolution Med Dent Sci. 2017;6(34):2798-800.

43. Paulozzi LJ, Erickson JD, Jackson RJ. Hypospadias trends in two US surveillance systems. *Pediatrics* 1997; 100:831–4.

44. Mai CT, Isenberg J, Langlois PH, Alverson CJ, Gilboa SM, Rickard R, Canfield M, Anjohrin SB, Lupo PJ, Jackson DR, Stallings EB, Scheuerle AE, Kirby RS for the National Birth Defects Prevention Network. Brief report, Population-based birth defects data in the United States, 2008 to 2012: Presentation of state-specific data and descriptive brief on variability of prevalence. Birth Def Res (Part A). 2015; 103:972-94.

45. Carmichael SL, Shaw GM, Laurent C, Olney RS, Lammer EJ, and the National Birth Defects Prevention Study. Maternal reproductive and demographic characteristics as risk factors for hypospadias. Paediatr Perinat Epidemiol. 2007; 21: 210–8.

46. Reefhuis J, Honein MA, Schieve LA, Correa A, Hobbs CA, Rasmussen SA, and the National Birth Defects Prevention Study. Assisted reproductive technology and major structural birth defects in the United States. Human Rep. 2009; 24:360–6.

47. Carmichael SL, Shaw GM, Laurent C, Croughan MS, Olney RS, Lammer EJ. Maternal progestin intake and risk of hypospadias. Arch Pediatr Adolesc Med. 2005;159: 957–62.