

Initial assessment of a child with suspected disorder of sex development

Asrar Ahmad,¹ Farrukh Ayub,² Irum Saleem,³ Nisar Ahmad⁴

Abstract

Disorders of sex development (DSD) are defined as discrepancy between chromosomal, gonadal and anatomic sex. The basic principles for the management of DSD include a multidisciplinary approach for gender assignment. Clinical assessment includes a detailed history and examination of external genitalia. Most of the disorders with symmetrical gonades indicate hormonal cause while asymmetrical gonades are found in chromosomal DSDs. Karyotyping will indicate a 46XX DSD, 46 XY DSD or mosaicism. Internal anatomy is defined by ultrasonography, genitoscopy and laparoscopy. Human chorionic gonadotrophins (hCG) stimulation test is carried out in under-virilised males to see the function of Leydig cells in testes. The Most common cause of 46XX DSD is congenital adrenal hyperplasia (CAH). The decision of gender assignment surgery is to be taken in a multidisciplinary environment and with informed consent of the parents. Most of 46 XX CAH patients, even if markedly virilised, and 46 XY complete androgen insensitivity syndrome are raised as females. Similarly, most of 5- α reductase deficiency and 17- β hydroxysteroid dehydrogenase deficiency patients are assigned to the male gender. The decision in cases of mixed gonadal dysgenesis and ovotesticular DSD is based on the development of external and internal genitalia. Patients with androgen biosynthetic defects, partial androgen insensitivity syndrome are usually assigned to the male gender.

Keywords: Disorders of sex development, Karyotyping, Genitoscopy, Laparoscopy, 5- α reductase, 17- β hydroxysteroid dehydrogenase.

Introduction

"To be human is to be physically sexed and culturally gendered," wrote Elizabeth Reis in 'Bodies in Doubt'. The birth of a baby is one of the most celebrated occasions in a family. The first question that the parents are usually asked is, "is it a boy or a girl?" Uncertainty about the sex of

baby is a painful situation for the parents and a medical emergency for the doctors. The birth of such a baby is considered a social stigma in our society and parents usually hesitate to disclose it to the family members or consult a doctor. Moreover, these disorders may be associated with multiple congenital anomalies.¹ The parental level of depression is proportional to the severity of ambiguity of genitalia.² Literature and guidelines on the subject suggest a number of sophisticated investigations like molecular genetics³ and hormonal precursors assays. Similarly, new genes are being discovered responsible for development of gonades.⁴ Most of these investigations are not even available in our tertiary care centres and we only have to rely on examination and karyotyping. Therefore, we have developed simple algorithms which are helpful in diagnosing most of these disorders.

Disorders of sex development (DSD) are defined as congenital conditions in which there is discrepancy between chromosomal, gonadal and anatomical sex.⁵ The prevalence of genital anomalies is usually one in 300 births⁶ but the birth prevalence of true genital ambiguity may be as low as one in 5000 births.⁷ In 2006, the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) published a consensus statement on management of intersex disorders and proposed the term 'DSD' instead of terms like 'intersex', 'pseudohermaphroditism (PH)', 'hermaphroditism', 'sex reversal' etc.⁸ (Table).

The basic principles for the management of DSD are⁹: Expert evaluation is necessary before gender assignment in newborns; Evaluation and management shall be done by a multidisciplinary team¹⁰ usually in a tertiary care centre; All newborns shall have either male or female sex assignment; There shall be open communication between parents, patient and the team; Concerns of the family shall be addressed in confidence.

The current methods employed for the diagnosis of DSDs include clinical assessment by history and physical examination, laboratory investigations like hormone levels and karyotyping and imaging.¹¹ In complex disorders diagnostic laparoscopy is also helpful to establish a therapeutic strategy.¹²

¹Consultant Surgeon, CMH Nowshera, ²Registrar Anesthesia, CMH Multan, ³Medical Officer Private Setup, ⁴Medical Officer, Hayat Abad Medical Complex, Peshawar.

Correspondence: Asrar Ahmad. Email: drasrar.ahmad@yahoo.com

Table: Disorders of Sex Development (DSD).

Sex chromosome DSD	46 XY DSD (Under-virilised male)			46 XX DSD (Virilised female)		
	Disorders of Androgen synthesis	Disorders of testicular development	Disorders of Androgen Action	Disorders of ovarian development	Disorders of androgen excess	
◆45 X Turner and variants ◆47 XXY Klinefelter and variants ◆45 X/ 46 XY MGD ◆Chromosomal ovotesticular DSD	◆Synthesis defect ◆LH receptor defect ◆5α reductase deficiency ◆Disorders of AMH ◆Endocrine disruptors ◆Cloacalexstrophy	◆Complete gonadal Dysgenesis ◆Partial gonadal dysgenesis ◆Gonadal regression ◆Ovotesticular DSD	◆Androgen insensitivity Syndrome ◆Partial ◆Complete	◆Ovotesticular-ar DSD ◆Testicular DSD ◆Gonadal Dysgenesis	CAH	Non CAH

CAH: Congenital adrenal hyperplasia.

LH: Luteinizing hormone.

AMH: Anti-mullerian hormone.

Clinical Assessment: In isolated cryptorchidism, a chromosomal anomaly may be present in approximately 3% cases, in hypospadias 7% and in a combination of cryptorchidism and hypospadias, in 13% cases.¹³ In infants with proximal hypospadias (penoscrotal, scrotal, perineal), detailed studies performed revealed a likely cause in 31% of cases.¹⁴ Infants with suspected DSD who require further clinical evaluation should include those with isolated perineal hypospadias, isolated micropenis, isolated clitoromegaly, any form of familial hypospadias and those who have a combination of genital anomalies with an external masculinisation score (EMS) of <11.¹⁵

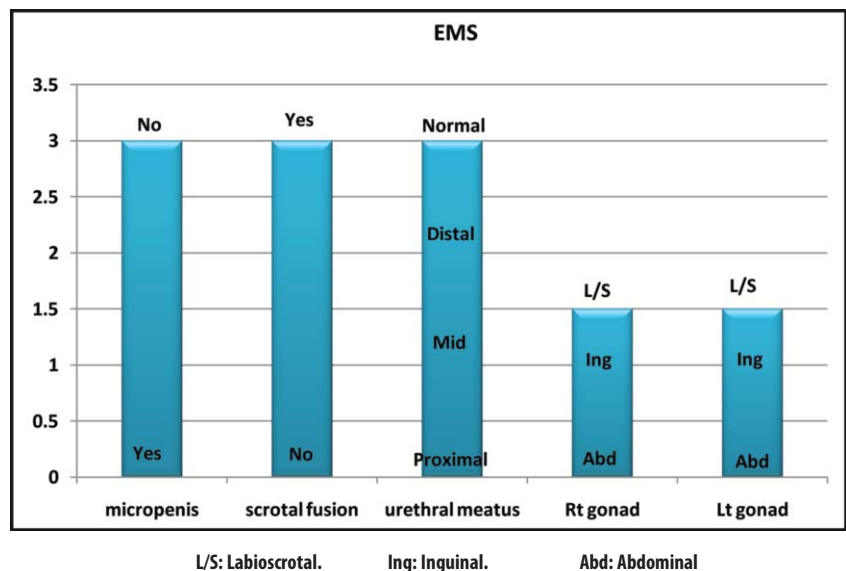
History: The history of drug use during pregnancy can cause virilisation of the female foetus. Similarly, maternal virilisation may be due to maternal androgen secreting tumour or aromatase deficiency. Family history of consanguinity or sudden deaths or other cases of DSD may indicate an autosomal recessive disorder.

Examination: Examination of the external genitalia shall include gonads, if palpable and symmetrical or not. Symmetry usually indicates hormonal cause while asymmetry is present in chromosomal DSD. The length of the phallus should be determined. The normal-term newborn penis length is about 3cm (stretched length from pubic tubercle to tip of penis) with micropenis less than 2 - 2.5cm, although it varies slightly depending on the ethnic origin. These external features can then be scored to provide the aggregate EMS score (Figure-1).

Routine systematic examination of 423 consecutive, apparently healthy, term newborn boys revealed that 412 (98%) had the maximum EMS of 12;10 had an EMS of 11: and only 1 of 423 had an EMS of <11. EMS <11 needs further evaluation.¹⁶

Similarly, for an apparent female the degree of virilisation shall be classified according to Prader's stages (Figure-2).¹⁷ Hyperpigmentation of the genital skin and nipples may occur due to excessive adrenocorticotrophic hormone (ACTH) in congenital adrenal hyperplasia (CAH).

Investigations: A baby with symmetrical gonads is most likely an under-virilised male and similarly absence of gonads and presence of uterus indicate a virilised female. In virilised female patients it is very important to check the serum 17-hydroxy progesterone (17-OHP) level and serum electrolytes. However, serum 17-OHP and serum

**Figure-1:** External masculinisation Score (EMS).

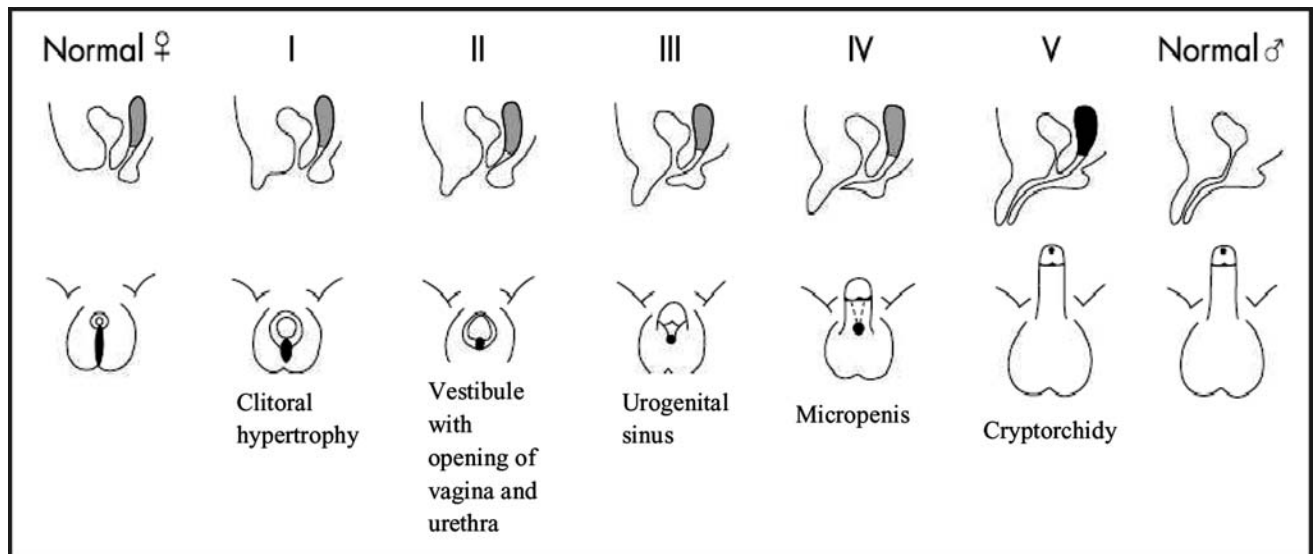


Figure-2: Prader's stages of virilisation.

electrolytes are not reliable before 36 hours and fourth day of life respectively, in salt losing CAH.⁹

Karyotyping: Barr bodies can be checked in XX chromosome cells as a rapid and screening test, but it is not reliable. Karyotyping gives the detailed information about the chromosomes but in most of the centres it takes more than 4 weeks. Polymerase chain reaction (PCR) for sex determining region on Y-chromosome (SRY) can be carried out in one working day.

Internal Anatomy: Ultrasonography is done for the presence of uterus, impalpable gonads in the inguinal canal, renal anomalies and adrenals. Examination under anaesthesia and genitoscopy shall be carried out to see the length of common channel in cases of CAH. Laparoscopy¹⁸ can be done for intra-abdominal gonads, biopsy and to rule out persistent mullerian duct syndrome (PMDS).

Human Chorionic Gonadotrophins (hCG) Stimulation Test:

In an XY under-virilised male, if both the gonads are symmetrical (either palpable or impalpable), the most likely cause is hormonal but if the gonads are asymmetrical the most likely cause is chromosomal (dygenesis). It is very important to check for functioning Leydig cells. The hCG stimulation test shall be performed when the serum testosterone levels are high usually from 4 weeks to three months of age.¹⁹ Basal testosterone levels are checked and then 1000-1500 IU (<1 year old, 500 units; 1-10 years, 1000 units; >10 years, 1500 units)¹⁴ of hCG are given intramuscularly (IM) daily for three days and the rise in testosterone level checked 24 hours after

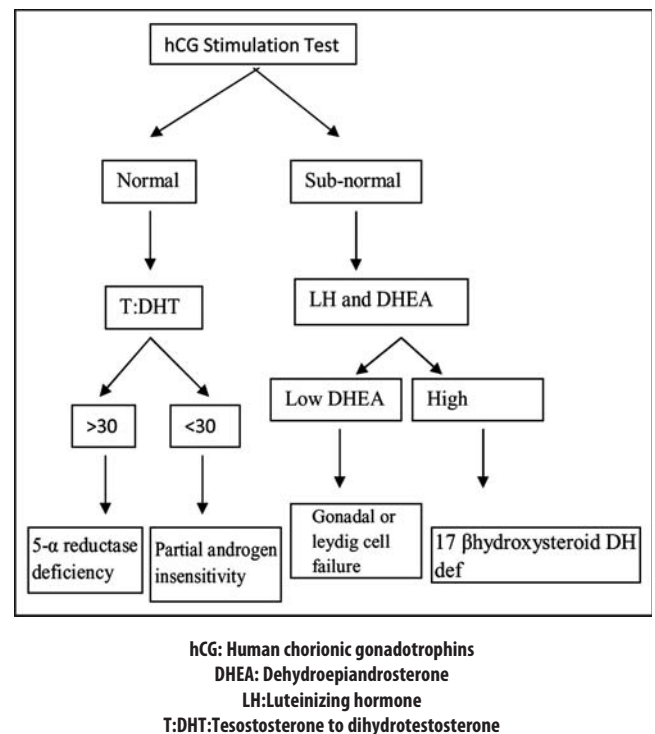


Figure-3: hCG Stimulation Test.

the last injection. At times when there is no response then 1500 IU are given 2 days a week for the next two weeks. A twofold rise above the basal level is considered normal.⁹ If the response is normal it means that there is 5-α reductase deficiency or partial androgen insensitivity. Total androgen insensitivity patients present with female

phenotype and amenorrhoea at puberty. In such cases if the ratio of testosterone to dihydrotestosterone (T: DHT) is ≥ 30 ,²⁰ it is suggestive of 5- α reductase deficiency. When the response is not normal it means that there is dysgenesis of gonads, vanishing testis syndrome, leydig cell hypoplasia or abnormality in the testosterone synthesis especially 17 β hydroxysteroid dehydrogenase deficiency. In such cases, serum luteinizing hormone (LH), dehydroepiandrosterone (DHEA) levels shall be checked. Low DHEA and high LH levels signify gonadal dysgenesis

or leydig cell hypoplasia while raised DHEA levels are suggestive of 17 β hydroxysteroid dehydrogenase deficiency (Figure-3).

Anti-mullerian hormone (AMH) level tests the function of sertoli cells and can also be used instead of hCG test. AMH may be undetectable in bilateral anorchia and may eliminate the need for surgical exploration of the testes.²¹

Histopathology: At times biopsy of the genital skin for mosaicism and 5 α -reductase activity and gonadal biopsy

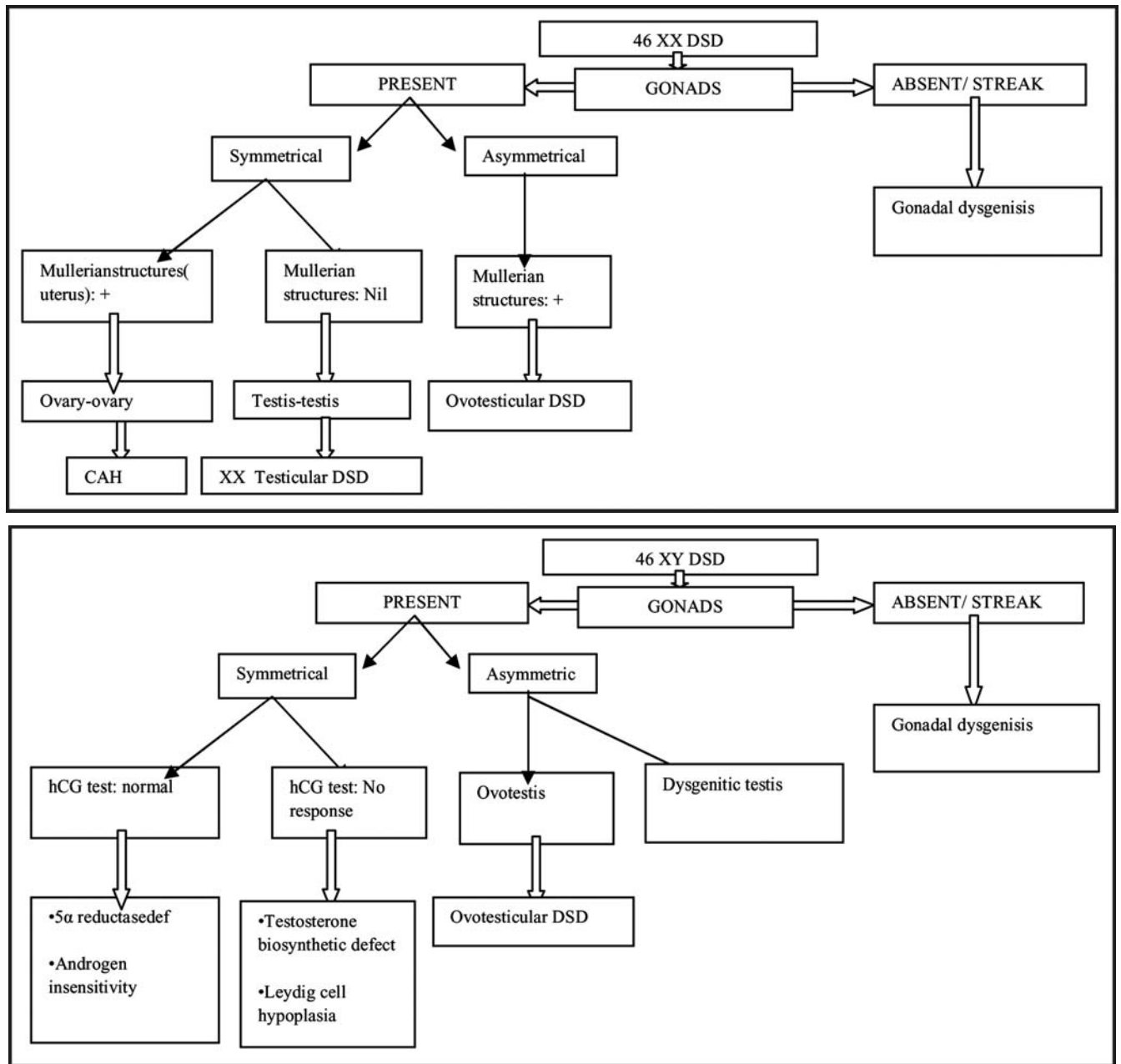


Figure-4: Algorithm for 46 XY DSD with ambiguous genitalia.

may be required in cases of mixed gonadal dysgenesis or ovotesticular DSD.

Aetiology

46XX DSD

The most common cause is CAH due to 21-hydroxylase deficiency (95%).²² Gonads are symmetrical ovaries and uterus is present. Serum 17-OHP levels are raised. The fertility potential is considered to be highest in this group of DSDs.²³ Other causes could be 11-hydroxylase deficiency, placental aromatase deficiency, exogenous steroids and maternal ovarian or adrenal tumours.

When the gonads are asymmetrical the most likely cause is ovotesticular DSD (true hermaphrodite), but in about 20% of the cases karyotype may be 46XX/46XY.¹⁸ Ovotestes with bipolar distribution of testicular and ovarian tissue is the most common type of gonad found in these children.²⁴ Rarely both the gonads may be testes (XX testicular DSD) (Figure-4).

46XY DSD

A 46 XY DSD with low basal testosterone level, low testosterone precursors and poor response on hCG stimulation test is suggestive of gonadal dysgenesis or lipoid CAH. If the gonadotrophins (LH level) are increased, it may suggest Leydig cell hypoplasia. Similarly, if the testosterone precursors are high with low basal and hCG stimulation testosterone levels, it indicates a defect in the biosynthetic pathway. A normal hCG test either suggests 5- α -reductase deficiency or androgen insensitivity syndrome. In the former T:DHT ratio is increased.

Gender Assignment

The decision of gender assignment and surgery is to be taken in a multidisciplinary environment and with informed consent of the parents. Some studies²⁵ have suggested assignment of sex based on the phenotype of the external genitalia. Most of 46 XX CAH patients, even if markedly virilised, and 46 XY complete androgen insensitivity syndrome are raised as females.^{26,27} Surgery include clitoroplasty, labioplasty and vaginoplasty²⁸ but almost 90% will only require vaginoplasty.²⁹ Patients of 5- α reductase deficiency³⁰ and 17- β hydroxysteroid dehydrogenase deficiency³¹ are assigned to the male gender. The decision in cases of mixed gonadal dysgenesis and ovotesticular DSD is based on the development of external and internal genitalia. Bilateral gonadectomy is recommended in children having mixed gonadal dysgenesis with intra-abdominal testes due to the high risk of development of gonadoblastoma.³² Patients with androgen biosynthetic defects, partial androgen insensitivity syndrome are usually assigned to the male

gender.³³ The optimum timing for feminising genitoplasty is not determined.³⁴⁻³⁵ On the other hand, it may be recommended to repair the ambiguous genitalia in males at 6 to 18 months of age.³⁶

Conclusion

The management of DSD cases shall include a multidisciplinary approach. In most of the cases a diagnosis can be reached by detailed history and examination and will not require sophisticated tests. Symmetrical gonads indicate hormonal cause while asymmetrical gonads are indication of chromosomal DSDs. Karyotyping may indicate a 46XX DSD, 46XY DSD or mosaicism. Ultrasonography, genitoscopy and laparoscopy may be done to define the internal anatomy. The hCG stimulation test is carried out in under-virilised males to see the function of Leydig cells in testes. The decision of gender assignment surgery is to be taken in a multidisciplinary environment and with informed consent of the parents.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Hutson JM, Grover SR, O'Connell M, Pennell SD. Malformation syndromes associated with disorders of sex development. *Nat Rev Endocrinol* 2014; 10: 476-87.
2. Wolfe-Christensen C, Fedele DA, Kirk K, Philips TM, Mazur T, Mullins LL et al. Degree of external genital malformation at birth in children with a disorder of sex development and subsequent caregiver distress. *J Urol* 2012; 188: 1596-600.
3. Atta I, Ibrahim M, Parkash A, Lone SW, Khan YN, Raza J. Etiological diagnosis of under virilized male/XY disorder of sex development. *J coll Physicians Surg Pak* 2014;24:714-8.
4. Ostrer H. Disorders of sex development (DSDs): an update. *The Journal of Clinical Endocrinology & Metabolism*. 2014;99:1503-9.
5. Hughes IA. Disorders of sex development: a new definition and classification. *Best Pract Res Clin Endocrinol Metab* 2008;22:119-34.
6. Ahmed S.F, Dobbie R, Finlayson A.R, Gilbert J, Youngson G, Chalmers J et al. Regional & temporal variation in the occurrence of genital anomalies amongst singleton births, 1988-1997, Scotland. *Arch Dis Childhood*.2004;89: 149-51.
7. Thyen U, Lanz K, Holterhus, Hiort O. Epidemiology and initial management of ambiguous genitalia at birth in Germany. *Hormone Research*.2006; 66:195-203.
8. Lee PA, Houk CP, Ahmed F, Hughes IA, and in collaboration with participants in the international consensus conference on intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology. Consensus statement on management of intersex disorders. *Pediatrics* 2006;118:488-500.
9. Consortium on the Management of Disorders of Sex Differentiation Clinical guidelines: for the management of disorders of sex development in childhood. [online] 2006 [cited 2018 Sep 3]. Available from: URL: <http://www.dsdguidelines.org/about/consortium>
10. Bangalore KK, Houk CP, Lee PA. Pragmatic approach to intersex,

- including genital ambiguity in the newborn. *Semin Perinatol*. 2017 ;41:244-51.
11. Moshiri M, Chapman T, Fechner PY, Dubinsky TJ, Shnorhavorian M, Osmon S et al. Evaluation and management of disorders of sex development: Multidisciplinary approach to a complex diagnosis. *Radiographics*. 2012 ; 32: 1599-618.
 12. Moriya K, Morita K, Mitsui T, Kitta T, Nakamura M, Kon M et al. Impact of laparoscopy for diagnosis and treatment in patients with disorders of sex development. *J Pediatr Urol*. 2014;10:955-61.
 13. Moreno-Garcia, M. & Miranda, E.B. Chromosomal anomalies in cryptorchidism and hypospadias. *J Urol* 2002;168: 2170-2.
 14. Boehmer, A.L.M., Nijman, R.J.M., Lammers, B.A.S. Etiological studies of severe or familial hypospadias. *J Urol* 2001;165: 1246-54.
 15. Ahmed SF, Achermann JC, Arlt W, Balen AH, Conway G, Edwards ZL. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. *Clin Endocrinol* 2011;75:12-26
 16. Ahmed, S.F., Khwaja, O. & Hughes, I.A. Clinical features and gender assignment in cases of male undermasculinisation: the role for a masculinisation score. *BJU Int* 2000; 85: 120-4.
 17. Prader A. Genital findings in the female pseudo-hermaphroditism of the congenital adrenogenital syndrome; morphology, frequency, development and heredity of the different genital forms. *Helv Paediatr Acta* 1954;9:231-48.
 18. Burgmeier C, Leriche C.J. Laparoscopy in the Surgical Treatment of Disorders of Sexual Development. *Laparoendosc Adv Surg Tech A*. 2016 ;9:730-3
 19. Ng KL, Ahmed SF, Hughes IA. Pituitary-gonadal axis in male undermasculinisation. *Arch Dis Child* 2000;82:54-8
 20. Ogilvy-Stuart AL, Brain CE. Early assessment of ambiguous genitalia. *Arch Dis Child* 2004;89:401-7.
 21. Teo AQ, Khan AR, Williams M.P, Carroll D, Hughes IA . Is surgical exploration necessary in bilateral anorchia? *J Pediatr Urol* 2013; 9: 78-81.
 22. Auchus RJ. The classic and nonclassic congenital adrenal hyperplasias. *Endocr Pract* 2015; 21: 383-9.
 23. Van BJP, Kolon TF. Fertility in disorders of sex development: A review. *J Pediatr Urol*. 2016; 12:418-25.
 24. Mao Y, Chen S, Wang R, Wang X, Qin D, Tang Y. Evaluation and treatment for ovotesticular disorder of sex development - experience based on chinese series. *BMC Urol* 2017 ;17:21.
 25. Jaruratanasirikul S, Engchaun V. Management of children with disorders of sex development: 2 years experience in southern Thailand. *World J Pediatr*. 2014;10: 168-74.
 26. Sturm RM, Durbin-Johnson B, Kurzrock EA. Congenital adrenal hyperplasia: current surgical management at academic medical centers in the United States. *J Urol* 2015;193: 1796-801.
 27. Clayton P E, Miller W L, Oberfield S E, Ritzen E M, Speisser P W. ESPE/LWPES CAH Working Group Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. *Horm Res* 2002;58:188-95.
 28. Wang LC, Poppas DP. Surgical outcomes and complications of reconstructive surgery in the female congenital adrenal hyperplasia patient: What every endocrinologist should know. *J Steroid Biochem Mol Biol* 2017; 165: 137-44.
 29. Mouriquand PD, Gorduza DB, Gay C-L, Meyer-Bahlburg HFL, Baker L, Baskin LS et al. Surger in disorders of sex development (DSD) with a gender issue: if (why), when, and how? *J Pediatr Urol* 2016; 12: 139-49.
 30. Mendonca BB, Batista RL, Domenice S, Costa EM, Arnhold IJ, Russell DW et al. Steroid 5 α -reductase 2 deficiency. *J Steroid Biochem Mol Biol*. 2016 ;163:206-11.
 31. Mendonca BB, Gomes NL, Costa EM, Inacio M, Martin RM, Nishi MY, et al. 46XY disorder of sex development due to 17 β -hydroxysteroid dehydrogenase type 3 deficiency. *Steroid Biochem Mol Biol*. 2017; 165(Pt A): 79-85.
 32. Liu AX, Shi HY, Cai ZJ, Liu A, Zhang D, Huang HF et al. Increased risk of gonadal malignancy and prophylactic gonadectomy: a study of 102 phenotypic female patients with Y chromosome or Y-derived sequences. *Hum reprod* 2014; 29: 1413-9.
 33. Mazur T. Gender dysphoria and gender change in androgen insensitivity or micropenis. *Arch Sex Behav* 2005; 34:411-421.
 34. Wolffenbuttel KP, Crouch NS. Timing of feminising surgery in disorders of sex development. *Endocr Dev* 2014; 27:210-21.
 35. Eckoldt-Wolke F. Timing of surgery for feminizing genitoplasty in patients suffering from congenital adrenal hyperplasia. *Endocr Dev*. 2014; 27:203-9.
 36. Springer A, Baskin LS. Timing of hypospadias repair in patients with disorders of sex development. *Endocr Dev* 2014; 27:197-202.