Indian Association of Pediatric Surgeons Guidelines on the Management of Differences in Sex Development

INTRODUCTION

The term DSD – disorders of sexual differentiation or differences in sex development – includes a variety of disorders, some of which manifest as “ambiguous genitalia” where the external genitalia is atypical. The new classification proposed is based on a molecular understanding of sex determination and development and is sensitive to sociocultural perspectives[1,2] as these conditions often cause significant emotional and psychological distress to the affected person and their family if not addressed sensitively.

At the outset itself, it must be understood that DSD patients have congenital malformation(s) and these subjects should not be clubbed or confused with trans-sexuals or transvestites. Further, the terms such as hermaphrodites, intersex disorders, and ambiguous genitalia have been discarded from the medical use and should not be used.

Although gender neutral upbringing and a third sex of rearing are accepted by the legal system in varying regions, the Indian sociocultural milieu and the parents require to have one of the two sexes (male or female) assigned for every newborn baby to provide a safe and socially secure upbringing.[3] Until views and norms of our society are radically transformed with education and self-realization, imposing laws or rules to ban all medically prescribed surgeries will force the parents resort to quackery to achieve their aims. Besides, this is a highly specialized field of pediatric surgical care where few subspecialists or centers manage these cases optimally, bringing together multiple disciplines in a cohesive and comprehensive manner. It is vital that children with DSD continue to receive required safe, effective medical care from qualified pediatric surgeons at such select centers. While this document aims to serve as a general guideline, the care of each child with DSD must be individualized.

A local multidisciplinary committee (LMDC) has a key role in this individualized decision-making. If no consensus is reached at LMDC, a state-level multidisciplinary committee (SMDC) will act as a nodal center to guide the LMDC.

LOCAL AND APEX MULTIDISCIPLINARY COMMITTEE

Local multidisciplinary committee

- DSD is to be managed only in centers with an LMDC
- The LMDC would comprise a minimum of three specialists
  - Pediatrician/pediatric endocrinologist
  - Pediatric surgeon
  - Child psychiatrist/child psychologist/or a pediatrician providing adolescent care.
- A medico-social worker and clinical geneticists may also be included, if available.
- All decisions on sex assignment and procedures should be done after thorough evaluation and discussion with LMDC and the parents/legal caretakers
- Minutes of such meetings should be documented and preserved.

State multidisciplinary committee

- SMDC is to be formed at state nodal center (apex institute), and it should comprise the following consultants: pediatric surgeon, pediatric endocrinologist, pediatric psychologist/psychiatrist, geneticist, and medico-social worker
- SMDC would keep a record of all cases sent by LMDC and act as a nodal center to decide on the
management of conditions where a decision is difficult
• It is recommended to keep a registry of all DSD cases at SMDC. Even cases where decisions have been made at LMDC, the minutes must be conveyed to SMDC for filing and records
• The e-mail/phone number of contact at SMDC should be available for all LMDC.

Apex multidisciplinary committee
• Apex multidisciplinary committee (AMDC) would be a national-level committee constituted by the Indian Association of Pediatric Surgeons whose members could be referred difficult cases by different SMDCs. This committee shall engage with the relevant ministries of Central Government and suggest reforms and policy matters for the DSD patients.

Differences in Sex Development Classification

Clinical Assessment and Evaluation
A basic initial clinical evaluation should include and documents the following details
• Appearance of genitalia – whether atypical [Table 1][4]
• Location of urethral meatus
• Phallic structure: Size (stretched flaccid phallic length, corporal body girth)
• Gonads: Location (bilateral nonpalpable/unilateral palpable or nonpalpable), consistency (firm/soft, homogeneous/heterogeneous)
• Genital folds: Labial/scrotal/labioscrotal; fusion of labioscrotal folds, anogenital ratio, and anogenital distance (posterior labial fusion)
• Presence of separate vaginal and urethral opening or single urogenital sinus
• Abdominal examination.

Standardized scores such as Prader Scale and External Masculinization Score should be used.

First tier of investigations in infants with atypical genitalia and/or bilateral impalpable gonads includes the following
• A screening ultrasonography to evaluate the presence of the uterus, gonads, and obstructive features (hydrometrocolpos, hydrenephrosis, etc.) that might endanger life
• Serum 17OH-progesterone (17OHP) and serum electrolytes
• The results of polymerase chain reaction or fluorescence in situ hybridization analysis using Y- and X-specific markers should be obtained as soon as possible. Conventional karyotyping is always performed to confirm the chromosomes.

Table 1: DSD Classification[4]

| 46XX DSD | 46XY DSD |
| --- | --- |
| Androgen excess: CAH, maternal exposure | Disorders of androgen synthesis - biosynthetic defects, conversion defects (5 alpha reductase deficiency, 17 beta HSD deficiency) |
| Disorders of ovarian development (gonadal dysgenesis) | AIS states - PAIS or CAIS |
| Disorders of testicular development (gonadal dysgenesis) | Sex chromosome DSD |
| 45XO/46XY (mixed gonadal dysgenesis) | 46XX/46XY (ovotesticular DSD) |

*Cases of CAIS, PMDS, vaginal atresia, cloacal exstrophy, turner/Klinefelter syndromes, and proximal hypospadias with bilateral palpable undescended testis may cause atypical genitalia in the newborn and will need specific evaluation. PMDS: Persistent Mullerian duct syndrome, CAH: Congenital adrenal hyperplasia, AIS: Androgen insensitivity, PAIS: Partial AIS, CAIS: Complete AIS, DSD: Differences in sex development, HSD: Hydroxy-steroid deficiency

• In centers where these facilities are not available, the neonate should be appropriately referred after stabilization
• In an infant with a combination of any of these: Karyotype of 46XX, significantly elevated serum 17OHP, typical electrolyte disturbances, and the presence of uterus: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency must be identified and managed expeditiously
• The identification and management of the other DSDs outlined below are comparatively less emergent.

Further evaluation
• Human Chorionic Gonadotrophin (hCG) stimulation test: When the karyotype is 46XY, a standard hCG stimulation is useful in differentiating the subtypes of XY DSD (testosterone [TST] biosynthetic defects, conversion defects, and AIS)
  • In gonadal dysgenesis/disorders of androgen synthesis – Elevated gonadotropins luteinizing hormone/ follicle stimulating hormone (LH/FSH), no increase in TST or dihydrotestosterone (DHT)
  • In AIS – Proportional increase in TST and DHT with low gonadotropins
  • In 5 alpha reductase deficiency (ARD) – Increase in TST but not DHT, elevated TST/ DHT ratio, low gonadotropins
• To identify gonadal details and Mullerian structural derivatives
  • Noninvasive imaging: Ultrasonogram/magnetic resonance imaging scan
  • Genitogram
  • Examination under anesthesia and requisite endoscopy (genitoscopy and laparoscopy), gonadal biopsy.
Standard, international diagnostic algorithms and nomograms are followed to complete the rational and scientific diagnostic process.

Guidelines for newborn

• Any sick newborn with ambiguous genitalia should be investigated on an emergency basis considering the life-threatening steroid crisis in CAH – the common form of DSD. Unexplained electrolyte imbalance with a history of loss of sibling in similar circumstances is strongly suggestive of CAH

• Whenever DSD is suspected, baseline investigations in consultation with pediatrician/endocrinologist are to be done, followed by a meeting arranged between the family and the team of experts as suggested for the LMDC. The aim of such a comprehensive meeting is to convey details about the suspected disorder and discuss the further line of management with the caretakers. This allays their fears and reduces the stress. The fact that the baby has a potential to be a functional member of the society is emphasized.

Parental Counseling and Gender Assignment

General principles

• Assigning a sex of rearing is a great responsibility and must be systematic

• The first conversations with the family need to set a positive tone. When addressing the infant, it is important to initially be gender neutral. Use “it/baby” instead of “he/she” that could inadvertently bias the family toward a gender

• Sex assignment decisions should be based upon information accrued from clinical examination, investigations, and multidisciplinary meetings. It takes into account the age at presentation; fertility potential; size of the phallus and sexuality issues; projected risk of pubertal virilization and associated gender dysphoria;[5] and parental/legal caretaker opinion/wishes

• When an older child presents where the family has already reared as a male/female, any decision for sex reassignment is made after extensive consultation with the child, the parents/caretakers about the scientific basis, future projections of medical issues, and pros/cons of reassigning the sex

• SMDC must be involved in situations where sex reassignment is sought

• If the child is >12 years, it is essential to involve the child in all decisions, and a verbal/written assent may be used for any procedures.

Sex assignment process in the neonatal period

Sex assignment process may be “noncontroversial” in conditions such as

• CAH – 46XX: There is a worldwide consensus on female sex of rearing; however, the timing of reconstructive surgery is still evolving

• Severe hypospadias with bilateral palpable testis – 46XY; there is worldwide consensus on male sex of rearing. The optimal age for correction is 9–18 months.

Sex assignment can be “difficult” in the following conditions

• Mixed genetic composition (XO/XX; XO/XY, XX/XY); or where there is disparity between genetic/composition and internal genital/gonadal anatomy (ovotesticular DSD, gonadal dysgenesis)

• In some XY DSD (conversion defects, PAIS) and pure/mixed gonadal dysgenesis (MGD) – It can be confusing. In these, the LMDC can decide on the sex of rearing after all information is available. When further clarification is needed, SMDC can be consulted.

General Principles of Gender Assignment in the Newborn

• CAH (XX karyotype; elevated 17OHP): Female sex is favored as they have normal female internal genitalia and fertility potential

• CAIS and pure forms of gonadal dysgenesis are raised as females with requirement for minimal surgical interventions in the future

• 46 XY conversion defects (5 ARD, 17 beta hydroxy-steroid deficiency [HSD] deficiency): These children usually virilize at puberty (phallic length increases; testicles descend). Hence, a male sex of rearing is favored

• 46XYY, PAIS: Sex of rearing may be determined by the phallic size and response to hCG during testing. The latter predicts the pubertal phallic growth with TST supplementation. Frequently, due to the small size of phallus, these children are reared up as girls. However, in those with androgen effects, male sex of rearing is possible

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• MGD (46, X/46, XY): Variable sex of rearing depending on proportion of dysgenic/functional internal gonad and external anatomy. Often, due to androgen effects (due to one functioning testis), virilization is manifested that may favor a male sex of rearing

• Ovotesticular DSD variable sex of rearing depends on internal and external anatomy. The fertility potential is better if reared as female.
Timing and Nature of Surgical Interventions in Differences in Sex Development

There is considerable debate as to the optimal timing of any genital surgery. Decisions about nature and timing of any surgery are made after discussions with the family and in the LMDC. At all stages, the following factors are considered – family concerns, psychological impact on the child, technical ease of reconstructive surgery, anesthetic issues of multiple-staged reconstructive surgery.\[6\]

Circumstances in which genital surgery is permissible

When a potentially “life-threatening” circumstances arise (e.g., sepsis/obstructive uropathy, risk of gonadal malignancy) on the child with DSD, the interest of the child is of paramount importance and a quick decision can be made, preferably in communication with the LMDC.

- DSD with retained menstrual or mucinous fluid or recurrent urine infection/urosepsis due to obstruction to outflow due to common urogenital channel requires urgency diversion procedures (minimally invasive/surgical), e.g., percutaneous nephrostomy, vaginostomy
- In children with certain forms of DSD (mixed gonadal dysgenesis with streak gonads, PAIS), the risk of cancer is high making it potentially “life-threatening.” Excision biopsy of streak/dysgenetic gonad. In PAIS/CAIS, gonads are kept until adolescence as malignant risk is minimal till such time and it aids spontaneous pubertal development
- Once sex of rearing has been conclusively decided, the incongruent gonadal tissue or genital duct (e.g., testicular tissue and vas deferens in ovotesticular DSD raised as females) can be removed with due informed consent.

Circumstances in which genital surgery is controversial

Congenital adrenal hyperplasia

- Often, proper steroid suppression suffices to control mild clitoromegaly in CAH. However, if severe refractory clitoromegaly and painful erection are an issue, LDMC/SMDC should consulted before the intervention
- There has been a move away from early vaginoplasty in childhood, and one may wait till puberty when a single-stage urovaginal reconstruction can be undertaken with informed consent of the adolescent. However, in cases where there are urinary infections or when there is obstruction to urogenital tract, early surgery may be required. The LMDC must be informed and early permission sought.
- CAH reared as boys or with overt masculine orientation/gender dysphoria: In this rare situation, SMDC may be consulted if a sex re-assignment is requested. If male sex identity is established, these children will need hysterectomy/gonadectomy that may be delayed until puberty when informed assent of the adolescent is obtained.

Risk of Germ Cell Malignancy

- Low risk: Turner syndrome (−Y) −1%, CAIS − 2%; ovotesticular DSD − 3%\[7\]
- Intermediate risk: Turner syndrome (with Y) −12%; 17 beta HSD − 28%; gonadal dysgenesis (scrotal gonad) − not known; PAIS (scrotal gonad) − not known
- Highest risk: Gonadal dysgenesis (with Y) − intra-abdominal gonad − 15%−35%; Denys-Drash (with Y) − 40%, PAIS (nonscrotal gonad) − 50%; MGD–Frasier syndrome − 60%.

Gender Dysphoria/Gender Identity Disorder

- Gender dysphoria is low in women with CAH (<5%), CAIS (<2%), and PGD (<5%)\[5\]
- Gender dysphoria is variable (25%−40%) in PAIS, MGD, ovotesticular DSD
- Gender dysphoria is high in women with 5 ARD/17 beta HSD (>50%).

Psychological Assessment, Gender Orientation Assessment, and Age of Consent

- Gender orientation instruments are available in all age groups
- Child psychologist or psychiatrist who is experienced in this field must be involved whenever indicated to aid in decision-making
- A child <12 years of age is not eligible for legal consent in Indian Law
- However, children aged 7–12 years can provide verbal assent and 12–18 years can provide written assent which can be obtained along with parental consent.

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