

Disorders of Sex Development

The following information is based upon the Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006 Aug;118(2):e488-500 and Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. Horm Res Paediatr 2016;85:158-180

For further information on UK guidelines relating to the initial evaluation of DSD in children refer to the following - Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015). Clin Endocrinol (Oxf). 2016 May; 84(5): 771–788.

The following information provides a short summary of disorders of sex development and is does not provide an in-depth review of this complex field

Nomenclature and definition

- Disorders of sex development (DSD) describe disorders in which development of chromosomal, gonadal, or anatomical sex is atypical ¹.
- Nomenclature such as 'intersex', 'hermaphrodite', and 'pseudohermaphrodite' are now out of date and confusing to parents and clinicians. In response to concerns regarding outdated and controversial terms, the Chicago Consensus held in 2005 recommended a new terminology termed *Disorders of Sex Development* (DSDs).
- The term DSD has a comprehensive definition including any problem noted at birth in which the genitalia are atypical in relation to the chromosomes or gonads.
- The karyotype is used as a prefix defining the classification of DSD e.g. 46 XY gonadal dysgenesis
- Further clinical classification based on a primary genetic defect is preferred when available because these could more clearly predict disease-specific outcomes.
- The estimated overall incidence of DSD is 1 in 4500 but individually each is rare ².
- Congenital adrenal hyperplasia (CAH) and mixed gonadal dysgenesis are the most common causes of DSD, constituting approximately over 50% of all cases of genital ambiguity in the newborn period ³.
- The incidence rate among subjects with 46,XY to have a DSD has been estimated to be 1 in 20,000 births. Ovotesticular DSDs have been estimated to occur in 1 of 100,000 live births ⁴
- The frequency of testicular or mixed gonadal dysgenesis is estimated at 1:10,000 ⁵

Management

A general approach to the management of DSD should adopt the following principles ¹

1. Gender assignment must be avoided before expert evaluation in newborns
2. Evaluation and long-term management must be performed at a centre with an experienced multidisciplinary team
3. All individuals should receive a gender assignment



4. Open communication with patients and families is essential, and participation in decision-making is encouraged
5. Patient and family concerns should be respected and addressed in strict confidence

The management of children with DSD is wholly multidisciplinary and involves the following specialists

- Paediatric Endocrinologist
- Neonatologist
- Urologist
- Geneticist
- Psychologist
- Gynaecologist

The team should develop a plan for clinical management with respect to diagnosis, gender assignment, and treatment options before making any recommendations ¹

Clinical evaluation

Criteria of physical findings suggestive of DSD include

- Overt genital ambiguity
- Apparent female genitalia with an enlarged clitoris, posterior labial fusion or an inguinal/labial mass
- Apparent male genitalia with bilateral undescended testes, micropenis, isolated perineal hypospadias, or mild hypospadias with undescended testis
- A family history of DSD
- A discordance between genital appearance and a prenatal karyotype

Later presentations in older children include

- Previously unrecognized genital ambiguity
- Inguinal hernia in a girl (e.g., complete androgen insensitivity)
- Delayed or incomplete puberty
- Primary amenorrhea or virilisation in a girl
- Breast development in a boy
- Gross or cyclic haematuria in a boy

A series of hormonal laboratory tests and imaging are used to determine the underlying cause of DSD. However, a specific molecular diagnosis is identified in less than 30% of cases of DSD. Occasionally a diagnostic laparoscopy may be required

Gender assignment

Gender assignment is challenging and must involve the whole team and in particular the family

Overall factors to be considered for male or female assignment included probable adult gender identity (considered most important, but only tentatively predictable), anticipated quality of sexual function, surgical options/indications/risks, fertility potential, evidence of foetal CNS exposure to androgens, gonadal malignancy risk and psychosocial factors (familial, social and cultural)

- In 46,XX CAH, 90% of individuals raised as females maintain an assigned female gender identity ⁶



- All patients with 46,XY complete androgen insensitivity syndrome (CAIS), are raised as females ⁷
- About 60% of 5 α -reductase-deficient patients assigned female gender in infancy and virilising at puberty and all assigned males live as males ⁸
- For patients with partial androgen insensitivity syndrome, androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with assigned genders in 25% of individuals ⁹
- The construct of gender identity and related theories of gender identity development involve a higher degree of complexity and may come into play during childhood and adolescent development in individuals with DSD and should be duly considered during childhood development

References

¹ Lee PA, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*. 2006 Aug;118(2):e488-500

² Sax L: How common is intersex? A response to Anne Fausto-Sterling. *J Sex Res* 2002;39:174-178

³ Thyen U, Lanz K, Holterhus PM, Hiort O: Epidemiology and initial management of ambiguous genitalia at birth in Germany. *Horm Res* 2006;66:195-203.

⁴ Nistal M, Paniagua R, Gonzalez-Peramato P, Reyes-Mugica M: Ovotesticular DSD (true hermaphroditism). *Pediatr Dev Pathol* 2015;18:345-352.

⁵ Skakkebaek NE, Rajpert-De Meyts E, Main KM: Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;16:972-978.

⁶ Dessens AB, Slijper FM, Drop SL. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Arch Sex Behav*. 2005;32 :389– 397

⁷ Mazur T. Gender dysphoria and gender change in androgen insensitivity or micropenis. *Arch Sex Behav*. 2005;34 :411– 421

⁸ Cohen-Kettenis PT. Gender change in 46,XY persons with 5-alpha-reductase-2 deficiency and 17-beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005;34 :399– 410

⁹ Migeon CJ, Wisniewski AB, Gearhart JP, et al. Ambiguous genitalia with perineoscrotal hypospadias in 46,XY individuals: long-term medical, surgical, and psychosexual outcome. *Pediatrics*. 2002;110(3) .

