

Congratulations!

It's a...



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The birth of a baby with ambiguous genitalia is a crisis for both the infant and the family. Excluding life threatening conditions, such as congenital adrenal hyperplasia (CAH) are a priority and the family need significant support with the loss of their child's clear gender identity.

There are many terms used to describe the condition of ambiguous genitalia. Genital anomalies occur in approximately one in 4500 births.¹ Recently the term Disorders of Sex Development (DSD)¹ has been proposed to replace terms such as hermaphroditism, pseudohermaphroditism, intersex, sex reversal and other gender-related terms to avoid the controversy associated with these terms.

Physiologically normal anatomical sex differentiation proceeds in an orderly way with each stage determining the next stage. Firstly there is chromosomal sex (46 XY or 46 XX), then gonadal sex (testis or ovary) followed by internal and external duct sex (male or female internal/external genitalia). This is followed by the sex of assignment, ie the term given to the baby (boy or girl), the sex of rearing (male or female) and the identification with one's gender (male or female). Finally, one develops sexual orientation or sexual preference.

Initially in normal fetal development, female and male have identical anatomy with an indifferent gonad, Mullerian and Wolffian ducts internally and a urogenital sinus leading to the exterior. In XX females the indifferent gonad becomes an ovary. If the gonad is an ovary (or if the gonad is absent), the Wolffian duct atrophies and the Mullerian ducts develop into the fallopian tubes, uterus and cervix, the urogenital sinus develops into the female phenotype with a vagina, labia and clitoris. In males, the SRY region on the Y chromosome contains a testis-determining factor which directs an indifferent gonad to develop into a testis. If the gonad is a testis, then it secretes Mullerian Inhibiting Hormone (MIH), causing regression of the Mullerian duct. Testosterone promotes development of the Wolffian duct into the epididymis, vas deferens and seminal vesicles.

In the urogenital sinus, testosterone secreted from the testis is converted into dihydrotestosterone, causing masculinisation of the urogenital sinus into a penis and scrotum.

Abnormalities of sexual differentiation or DSD have many causes and presentations. Following the above schema, these causes may be chromosomal, gonadal or due to abnormalities in urogenital sinus development. The virilised female or 46XX sex reversal may be caused by androgen exposure, such as due to accidental androgen ingestion by the mother who may not be aware of her pregnancy (eg danazol treatment) or a maternal androgen secreting tumour. More commonly virilisation may be due to excessive androgens formed by the fetal adrenal glands, as occurs in the fetus which has CAH or an aromatase enzyme deficiency.

Undervirilised males or 46XY sex reversal may be due to dysplastic or hypoplastic testes, due to fetal lutenizing hormone (LH) deficiency or an LH receptor mutation. Undervirilisation could be due to testosterone synthesis defects or failure of testosterone activation or androgen insensitivity syndromes (AIS), previously called Testicular Feminisation syndrome.

Complete and incomplete forms of DSD may occur. They may be due to isolated deficiency of MIH, as occurs with 46 XY males with a uterus. Other chromosomal defects may cause a variety of possible effects. Absence of part of the Y may yield a 46 XY infant with female phenotype and streak ovaries. Transfer of part of the Y onto an X may yield a 46 XX infant with male phenotype and testes.

The initial examination of a child with DSD requires a close examination of the perineum and classification of the examination (see Figure 1). This is best done by staging the perineal findings according to the Prader classification (Figure 2).

The clinical management of a child with DSD requires sensitivity and a staged investigative approach. There will be an initial process to determine the cause of the disorder then, potentially in many cases, a lifetime of ongoing care either hormonal and/or surgical. The approach is outlined in Figure 3.

The causes of DSD are multiple, however, the majority of virilised 46 XX infants will have CAH. In contrast, only 50 per cent of 46 XY children with DSD will receive a definitive diagnosis.² CAH presents with salt-losing state and ambiguous genitalia in the newborn

Perineal physical examination features that suggest DSD include:

- Overt genital ambiguity (eg cloacal exstrophy)
- Apparent female genitalia with an enlarged clitoris, posterior labial fusion, or an inguinal/labial mass
- Apparent male genitalia with micropenis, isolated perineal hypospadias or mild hypospadias with undescended testis or bilateral undescended testes
- Discordance between genital appearance and a prenatal karyotype

Figure 1

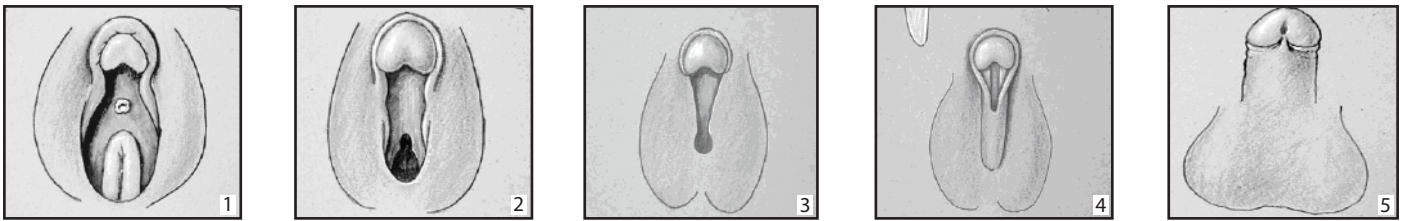


Figure 2: Prader classification 1 to 5. 1) Female external genitalia with clitoromegaly; 2) Clitoromegaly with partial labial fusion forming a funnel-shaped urogenital sinus; 3) Increased phallic size with complete labioscrotal fusion forming a urogenital sinus with a single opening; 4) Complete scrotal fusion with the opening of the urogenital sinus at the base of the phallus; 5) Normal male external genitalia.

female and normal to enlarged genitalia in the male. The salt loss causes failure to thrive, dehydration, low serum sodium and high potassium. Hypoglycaemia and shock are other presentations of CAH. On examination, the infant may have increased pigmentation especially of the scrotum/labia or nipples (due to elevated ACTH). The incidence of CAH is one in 10,000 in severe forms and one in 100 to one in 1000 in milder forms, depending upon the population.⁴ It is caused by a mutation of a steroidogenic enzyme gene and results in defective cortisol production. The most common forms are 21-hydroxylase deficiency (98 per cent), 11 β -hydroxylase (one per cent), 3 β -hydroxy steroid dehydrogenase (rare), 17-hydroxylase deficiency (rare), cholesterol desmolase (rare) and steroidogenic acute regulatory (StAR) protein (rare). The diagnosis of salt-losing CAH is made by the characteristic serum electrolyte pattern and elevated serum 17 OH-progesterone, elevated androgens and low serum cortisol.²

Most causes of DSD are recognised in the neonatal period. Later presentations of DSD in older children and young adults may take on many forms. The older child may have unrecognised genital ambiguity; delayed or incomplete puberty; an inguinal hernia in a female; virilization in a female or primary amenorrhea; breast development in a male or gross and occasionally cyclic hematuria in a male.¹

Gender assignment in newborns is determined by the genital appearance, diagnosis and genital surgical options. The need for lifelong medical therapy and the potential for fertility, the views of the family and circumstances relating to cultural practices are important to consider in this process of assigning gender. Available data supports male rearing in all patients with micropenis.¹

Surgical management is performed by a paediatric surgeon who has expertise in the care of children and specific training in the surgery of DSD. The process may be staged from infancy to adulthood depending on the genital anatomy. Surgery for less severe clitoromegaly is not frequently undertaken and should only be considered in cases of severe virilisation (Prader III, IV and V).^{5,6} The risk of disruption to orgasmic function and erectile sensation may need to be weighed up when considering clitoral surgery. The surgical procedure should be anatomically based to preserve erectile function and the innervation of the clitoris.^{5,6} The range of normal genital appearance is extremely broad. Emphasis is on functional outcome, rather than a strictly cosmetic appearance.

There are a number of indications for bilateral gonadectomy¹ to be performed in early childhood. The risk of future gonadal malignancy or the influence of testosterone exposure in females with gonadal dysgenesis and Y chromosome material are two such indications. Patients with androgen biosynthetic defects who are raised as female should also have gonadectomy before puberty. A scrotal testis in patients with gonadal dysgenesis is also at risk for malignancy and should be removed.

In conclusion, the loss of a clear gender identity at birth is a medical emergency and often a crisis for the family. It is important to consider the normal sex differentiation when investigating the cause of disorders of sex differentiation, however – above all – the psychological and emotional support of the family and child remains paramount.

References

1. Hughes I A, Houk C, Ahmed S F, Lee P A and LWPES/ESPE Consensus Group. Consensus statement on management of intersex disorders. *Arch Dis Child*. 2006; 91: 554-563.
2. The Children's Hospital at Westmead Handbook 1999.
3. Brown J, Warne G. Practical management of the intersex infant. *J Pediatr Endocrinol Metab*. 2005; 18: 3-23.
4. Grumbach M M, Hughes I A, Conte F A. Disorders of sex differentiation. In: Larsen P R, Kronenberg H M, Melmed S, et al, editors. *Williams textbook of endocrinology*, 10th edition. Philadelphia: W B Saunders, 2003: 842-1002.
5. Eroglu E, Tekant G, Gundogdu G, et al. Feminizing surgical management of intersex patients. *Pediatr Surg Int*. 2004; 20: 543-7.
6. Alizai N, Thomas D F M, Lilford R J, et al. Feminizing genitoplasty for congenital adrenal hyperplasia: what happens at puberty? *J Urol*. 1999; 161: 1588-91.

The clinical management of a child with DSD^{1,2}

1. Use non specific gender language: terms like 'your baby' or 'your child'.
2. Encourage the family to await confirmation of gender before giving the child a gender differentiating name.
3. Urgent expert consultation from experienced multidisciplinary team which would include a paediatric endocrinologist, a surgeon/urologist, a geneticist, neonatologist and social worker, and later a gynaecologist, medical ethicist and psychologist/psychiatrist.
4. General physical examination with attention to any associated dysmorphic features and an assessment of the genital anatomy needs to be carried out.
5. Perform chromosome determination with a karyotype.
6. Perform pelvic and abdominal ultrasound and x-ray studies of genital tract (genitogram) to delineate internal anatomy.
7. Exclude CAH in a virilised female (check electrolytes and measure serum 17-OHP and cortisol).
8. Appropriate hormone studies to assess testicular/ovarian/pituitary function.
9. Sex assignment (take into account ability of male to be functional).
10. The child may need therapy to achieve successful sex assignment (surgery, hormonal therapy).
11. Importantly, give regular and frequent counselling to both parents, including discussing with the parents what information to share in the early stages with family members and friends. Parents need to be informed about normal sexual development.