CHAPTER 99
DISORDERS OF SEX DEVELOPMENT

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Introduction

Sexual differentiation is the process of development of the differences between male and female from an undifferentiated zygote (fertilised egg). Sex and gender are both important determinants of health. The term "gender" describes those characteristics of females and males that are largely socially created, whereas "sex" encompasses those characteristics that are biologically determined.

Disorders of sex development (DSDs) have been endorsed by the Chicago Consensus to replace the term "intersex". The proposed changes in terminology are summarised in Table 99.1. DSD is defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical. Approximately 1 in 2,000 children globally is born with a DSD condition. This term uses chromosomes, rather than gonads, as the most important classifier of an individual's sex. In some DSDs, there is an associated obvious genital ambiguity at birth, whereas in others, the external genitalia are typically male or typically female, but the internal anatomy is discordant. Associated endocrinal and other congenital anomalies are always present.

Table 99.1: Proposed revised nomenclature.

Previous	Proposed
Intersex	DSD
Male pseudohermaphrodite, undervirilisation of an XY male, and undermasculinisation of an XY male	46,XYDSD
Female pseudohermaphrodite, overvirilisation of an XX female, and masculinisation of an XX female	46,XXDSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

DSDs are always challenging to manage. Choosing the optimal gender is difficult when the genitalia are ambiguous. There is the risk that childhood and adolescence for affected individuals will be compromised by gender dysphoria "dissatisfaction" (unhappiness with assigned sex, which occurs more frequently in individuals with DSD than in the general population, but is difficult to predict from karyotype, prenatal androgen exposure, degree of genital virilisation, or assigned gender). In addition, psychosexual difficulties, defined and noted to be influenced by factors including androgen exposure, sex chromosome genes, brain structure, social context, and family dynamics, may carry over into adult life.

Demographics

DSDs occur more commonly in developing countries. Certain areas of the world have a high incidence for certain genetic forms of DSD (see section on "Aetiology and Classification" for a discussion of gene deficiencies). 5α-reductase deficiency was first reported on one island in the Dominican Republic. It is also prevalent in southern Lebanon and the Eastern Highlands Province of Papua New Guinea, but is relatively rare in caucasians. 17β-Hydroxysteroid dehydrogenase deficiency is very common in the Gaza Strip. Both of these conditions can lead to a gradual transition in gender identity from female to male. In southern African blacks, 46,XX ovotesticular DSD has an unusually high prevalence.

Important Considerations in Africa and Developing Countries

Traditional Values and Beliefs

Traditional values and beliefs are often strong in certain cultures. They can play a very crucial role, especially in situations such as those presented by DSD, which is difficult to explain scientifically and poorly understood by the common man. This is often compounded by the fact that sexual issues are taboo subjects in certain societies, and parents do not want to discuss them even with medical professionals. Resorting to faith healers, shrines, and purveyors of magic is more natural for some cultures.

Family Issues

The lack of social security provisions in developing countries means that when they are no longer able to do productive work, parents are totally dependent on their children for survival. In many cultures, the eldest son has special responsibilities for both the physical and spiritual welfare of his parents; this is one powerful reason why sons may be valued more highly than daughters.

Consanguinity

Conditions such as congenital adrenal hyperplasia (CAH), which are perpetuated by autosomal recessive inheritance, are likely to affect multiple family members and to occur with greater frequency in countries where consanguinity is common.

Discrimination

It is extremely common for parents of children with DSDs to experience guilt, anxiety, and depression after the diagnosis has been made. Their natural reaction is to keep the child's condition a closely guarded secret, even from close relatives. This serves to further isolate these children and aggravate their distress. The parents' fear is that if the child's condition becomes widely known, both they and the child will suffer from being the subjects of rumour and discrimination.

Table 99.2: Classification of DSD.

Sex chromosome DSD	46,XY DSD	46,XX DSD
45,XO (Turner syndrome and variants)	*Disorders of gonadal (testicular) development* 1. complete gonadal dysgenesis (Swyer syndrome) 2. partial gonadal dysgenesis; 3. gonadal regression 4. ovotesticular DSD	*Disorders of gonadal (ovarian) development* 1. ovotesticular DSD 2. testicular DSD (e.g., SRY_, duplicate SOX9) 3. gonadal dysgenesis
47,XXY (Klinefelter syndrome and variants)	*Disorders in androgen synthesis or action* 1. androgen biosynthesis defect (e.g., 17-hydroxysteroid dehydrogenase deficiency, 5αRD2 deficiency, StAR mutations) 2. defect in androgen action (e.g., CAIS, PAIS) 3. luteinising hormone receptor defects (e.g., Leydig cell hypoplasia, aplasia) 4. disorders of anti-Müllerian hormone and anti-Müllerian hormone receptor (persistent Müllerian duct syndrome)	*Androgen excess* 1. foetal (e.g., 21-hydroxylase deficiency, 11-hydroxylase deficiency) 2. foetoplacental (aromatase deficiency, POR _P450 oxidoreductase_) 3. maternal (luteoma, exogenous, etc.)
45,XO/46,XY (MGD, ovotesticular DSD)		*Other* (e.g., cloacal exstrophy, vaginal atresia)
46,XX/46,XY (chimeric, ovotesticular DSD)		

Notes: CAIS = complete androgen insensitivity syndrome; DSD = disorder of sex development; MGD = mixed gonadal dysgenesis; PAIS = partial androgen insensitivity syndrome; StAR = steroidogenic acute respiratory (protein function).

Aetiology and Classification

Abnormalities of sex determination and differentiation result from mutations of any of the genes involved in male or female sex development. Some of these mutations are well-established, but additional mechanisms remain to be described. In addition to the adequate expression of these genes, proper timing of their expression is also important. For example, normal but delayed androgenic effects result in incomplete masculinisation of genitalia, whereas the persistent presence of Müllerian remnants results from normal but delayed Müllerian-inhibiting substance (MIS) action. For clinical purposes, DSDs are classified according to karyotype and based on the various steps of sex differentiation and development (Table 99.2).

Sex Chromosome DSD

The peripheral karyotypes of sex chromosome DSD show marked variation. Approximately 60% are 46,XX; 15% are 46,XY; and 25% show various forms of mosaicism. Less than 1% show 46,XX/46,XY chimerism or the existence of two or more cell lines, each of which has a different genetic origin.

DSDs and sex chromosome aneuploidy

In Klinefelter (47,XXY) and 47,XYY syndromes, normal male external genitalia are typically present at birth. However, rare cases of the syndromes have presented with ambiguous genitalia. In newborns affected by the Turner (45,XO) syndrome, the external genitalia appear female, regardless of whether the remaining X chromosome is maternal or paternal in origin. Rare cases of genital ambiguity observed with the Turner syndrome are probably related to a hidden 46,XY cell line.

Ovotesticular DSD

Ovotesticular DSD refers to the presence of a gonad that contains both ovarian follicles and testicular tubular elements in the same individual. Ovotestes are the most frequent gonad present in sex chromosome DSD (60%), followed by the ovary and then the testis (Figures 99.1 and 99.2). Most newborns with ovotesticular DSD possess a 46,XX chromosome complement and present with ambiguous genitalia; however, some possess a 46,XY chromosome complement or 46,XX/46,XY mosaicism. In newborns with ovotesticular DSD, the risk of germ cell tumours is believed to be low (3%) and no recommendation of testicular tissue removal is offered at this time.

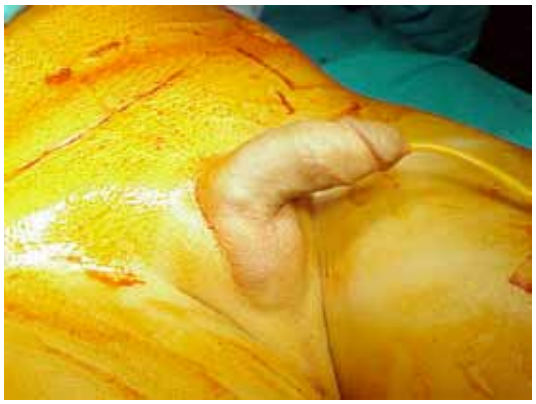

Figure 99.1: Ovotesticular DSD.

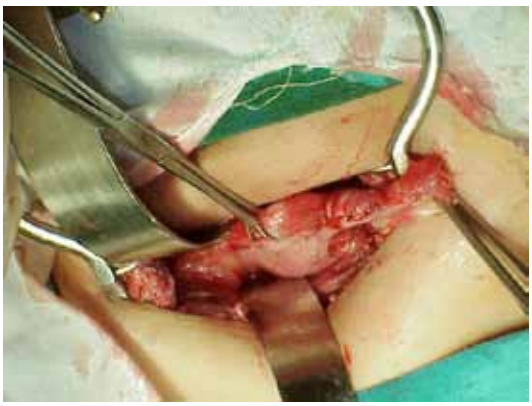

Figure 99.2: Müllerian remnant and ovotestis.

Mixed gonadal dysgenesis

Also known as asymmetrical gonadal differentiation, mixed gonadal dysgenesis is characterised by unique anatomical abnormalities. On one side of the body, a poorly developed testicular gonad exists, usually accompanied by wolffian duct structures. On the other side of the body is a gonadal streak. Most patients with mixed gonadal dysgenesis

have deficient testosterone production related to their poorly developed testicular gonad, resulting in ambiguous external genitalia. These cases can be considered a subgroup of the larger group of partial gonadal dysgenesis. Newborns affected by mixed gonadal dysgenesis can present with a 46,XY karyotype, but they can also present with a 45,XO/46,XY karyotype. Gonadectomy is recommended for these patients, regardless of whether they possess a 46,XY or 45XO/46,XY chromosomal complement.

46,XY DSD

Ambiguous genitalia in a 46,XY newborn are due to either abnormal formation of the early foetal testes, low production of testosterone, deficient 5α-reductase activity, or the inability to respond to androgens (androgen insensitivity syndrome). Depending on the degree of abnormality, clinical presentation of the external genitalia can be categorised according to the following phenotypes: female-appearing, ambiguous genitalia with a small phallus and hypospadias, or a micropenis without hypospadias.

46,XY DSD due to disorders in gonadal development

Gonadal dysgenesis is defined as an impairment of the formation of the primordia of the gonads involving the two major elements of the foetal testes, the Sertoli cells that secrete MIS, and the Leydig cells that secrete testosterone. Gonadal dysgenesis can result from a mutated or deleted SRY gene.

Complete gonadal dysgenesis in 46,XY DSD (Swyer syndrome)

Complete gonadal dysgenesis is characterised by a total absence of functional testicular tissue in a 46,XY newborn resulting in the inability to produce both testosterone and MIS. Newborns affected by complete gonadal dysgenesis present with fully formed Müllerian structures, bilateral streak gonads, and female external genitalia. Affected newborns are reared as females as a result of their female genital phenotype. Gonadectomy is recommended.

Partial gonadal dysgenesis in 46,XY DSD

In partial gonadal dysgenesis, it is presumed that a gene mutation results in a partial abnormality of testicular formation from the early urogenital ridge or bipotential gonad. Partial gonadal dysgenesis could also involve a mutation of a gene such as SRY needed to differentiate the bipotential gonads into testes. The phenotypic result of this particular category of DSD is partial masculinisation of the external genitalia along with variable degrees of Müllerian and wolffian duct maintenance and development.

Mixed gonadal dysgenesis in 46,XY DSD and 45,XO/46,XY DSD

This condition has been discussed previously under the heading "Mixed gonadal dysgenesis".

Embryonic testicular regression syndrome

In embryonic testicular regression syndrome (ETRS), most of the patients present with ambiguous genitalia or severe micropenis associated with complete regression of testicular tissue in one or both sides. The variable degree of masculinisation of the internal and external genitalia is a consequence of the duration of testicular function prior to its loss. Familial cases have been reported, but the nature of the underlying defect is still unknown.

Disorders in androgen synthesis or action

46,XY DSD due to deficiency of testosterone biosynthesis

Complete testosterone biosynthetic defect in 46,XY DSD refers to a complete inactivity of any of the enzymes required for the biosynthesis of testosterone from cholesterol. Similar to complete gonadal dysgenesis, newborns affected by a complete testosterone biosynthetic defect are typically reared female as a result of their female external genital phenotype. Partial testosterone biosynthetic defect in 46,XY DSD refers to conditions in which there is reduced activity of any of the enzymes required for the biosynthesis of testosterone from cholesterol. Similar to partial gonadal dysgenesis, a partial testosterone biosynthetic defect results in ambiguous external genitalia and variable degrees of wolffian duct development. However, unlike partial gonadal dysgenesis, Müllerian ducts are not maintained in newborns with a partial testosterone biosynthetic defect.

46,XY DSD due to 5α-reductase-2 deficiency

Deficiency of the 5α-reductase enzyme results from mutations in the steroid 5α-reductase type 2 (SRD5A2) gene. Affected newborns possess fully functioning Leydig and Sertoli cells, but due to the inability to convert testosterone to dihydrotestosterone (DHT), they present with undermasculinised external genitalia. The phenotype can range from a clitoral-like phallus with labio-scrotal folds to a penile urethra with testes located in the inguinal canal. At puberty, the testes of affected individuals are capable of spermatogenesis because, unlike testosterone, DHT is not required for germ cell maturation. Therefore, fertility is possible with the use of intrauterine insemination, and as a result, male sex rearing is recommended.

46,XY DSD due to a defect in androgen action

A defect in androgen action is either complete or partial, which is due to androgen receptor (AR) gene mutations. Newborns with complete androgen insensitivity syndrome (CAIS) present with female external genitalia and are therefore raised as girls. These newborns possess normally functioning testes, but they are unresponsive to the androgenic effects of their testosterone. Due to the risk, albeit low (<5%), of germ cell malignancy, removal of both testes following the completion of pubertal breast development is advised. After the testes are removed, estrogen replacement is required to maintain secondary sexual characteristics and to protect against osteoporosis. Individuals with partial androgen insensitivity syndrome (PAIS) experience variable degrees of end-organ unresponsiveness to androgens, resulting in variable degrees of wolffian duct and external genital ambiguity. Newborns affected by PAIS are considered to be at high risk (50%) for developing gonadal tumours, and bilateral gonadectomy is recommended at the time of diagnosis.

Luteinising hormone receptor defects in 46,XY DSD

Leydig cell aplasia or hypoplasia can be considered as a variant of gonadal dysgenesis. It is a condition of decreased numbers of Leydig cells, which leads to a decrease in androgen production. The phenotype resulting from Leydig cell hypoplasia is incomplete masculinisation of the external genitalia accompanied by incomplete development of the wolffian ducts.

Congenital micropenis without hypospadias in 46,XY DSD

Congenital micropenis refers to a penis that forms normally during the first trimester of foetal development, followed by a failure to lengthen in an appropriate manner during the second and third trimesters. In male newborns, a stretched penile length of 1.9 cm or less without hypospadias is considered a micropenis.

46,XX DSD

A foetus with a 46,XX chromosomal complement and normal ovarian organogenesis can be exposed to excessive amounts of androgens originating either from the foetus itself or from the mother. Timing of exposure is important. If androgen exposure occurs after the 8th week of gestation but before the 12th week, the vaginal opening may fuse posteriorly and appear slitlike. Exposure to androgen after the 12th week of gestation (e.g., exogenous administration to the mother) will result in clitoromegaly without fusion of the labioscrotal folds. On occasion, multiple congenital malformations may be present in a 46,XX newborn with ambiguous genitalia.

Abnormal foetal androgen production: congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a family of inherited disorders of adrenal steroidogenesis due to a mutation of one of the enzymes necessary for the biosynthesis of cortisol from cholesterol (Table 99.3). These abnormalities result in increased adrenocorticotropic hormone (ACTH) secretion by the pituitary gland that can, in turn, result in the

Table 99.3: Congenital adrenal hyperplasia.

Deficiency	Newborn Phenotype	Postnatal Virilisation	Other
StAR (steroidogenic acute regulatory protein function, also called lipoid congenital adrenal hyperplasia)	Infantile female	–	Salt loss
3ß-Hydroxylase	Ambiguous in XY and XX	+	Salt loss
17α-Hydroxylase (P450c17)	Infantile female	–	Delayed puberty
11ß-Hydroxylase (P450c11 ß)	Male in XY, ambiguous in XX	+	Hypertension
21 Hydroxylase (P450c21) (most common form)	Male in XY, ambiguous in XX	+	Salt loss
18 Hydroxylase (P450c11B2)	Normal	–	Salt loss

increased secretion of cortisol precursors and adrenal androgens. CAH is considered to exist in classic (salt wasting and simple virilising) and nonclassic forms.

Classic CAH

Males with classic CAH may not be diagnosed clinically at birth because they do not have genital ambiguity except for scrotal hyperpigmentation and phallic enlargement. Virilisation in boys due to CAH is distinguished from true precocious puberty by the testicular size, which is <4mls in prepubertal boys affected with CAH.

Females with classic CAH due to salt wasting or simple virilising forms will have virilised genitalia at birth, ranging from clitoral enlargement, rugated labioscrotal folds (with or without posterior fusion; Figure 99.3), to complete fusion of labioscrotal folds, urogenital sinus, and a single opening typical of a male (Figure 99.4).

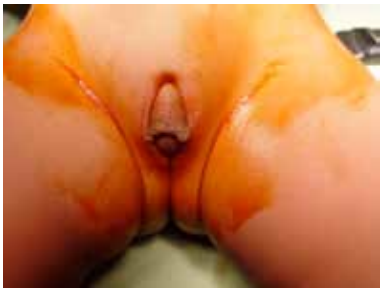

Figure 99.3: Classic CAH.

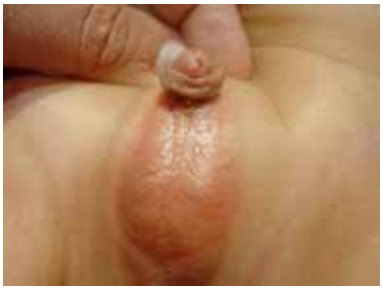

Figure 99.4: Severe virilisation.

Inadequate secretion of the mineralocorticoid aldosterone causes salt wasting in approximately three-quarters of all classic CAH patients. It is characterised by hyponatremia, hyperkalemia, inappropriate natriuresis, and low serum and urinary aldosterone with concomitantly high plasma renin activity. Affected male newborns with the salt-wasting phenotype usually are undiagnosed at birth, and they present 2–3 weeks later or earlier, if stressed, in salt-wasting adrenal crisis.

Simple virilising is prenatal virilisation and progressive postnatal masculinisation with accelerated growth and advanced bone ages but no evidence of mineralocorticoid deficiency. Affected males with the simple virilising form, if not diagnosed at birth, will present at 2 years of age or older with early development of pubic, auxillary, and facial hair, penile enlargement, body odor, and growth acceleration with bone age advancement.

Nonclassic CAH

Nonclassic 21-hydroxylase deficiency is one of the most common autosomal recessive diseases in the world. This form of CAH results from a mild deficiency of the 21-hydroxylase enzyme and is diagnosed by serum elevations of 17-hydroxypregnenolone (within the range of levels for unaffected individuals and levels observed for classic CAH patients). Patients with nonclassic CAH do not have symptoms at birth. Clinical presentation during childhood may include early pubic hair development, growth acceleration, and bone age advancement. Hirsutism is the most common symptom (60%), followed by irregular menses (54%), and acne (33%) in adolescent or adult women with nonclassic CAH.

Excess maternal androgen production

Because excessive androgen production adversely affects fertility due to anovulation, cases of maternal androgen production during pregnancy are extremely rare. The origin of these maternal androgens is usually the ovaries or adrenal glands.

Placental aromatase deficiency

During foetal development, the adrenals produce large amounts of 17-hydroxypregnenolone and 16-hydroxy-DHA. These steroids are transferred to the placenta, which then converts these steroids into androgens and then estrogens. If an aromatase enzyme deficiency exists, then androgen precursors accumulate and return to foetal circulation, resulting in masculinisation of female foetuses.

Clinical Presentations of DSD

DSDs may cause changes that are immediately visible in the newborn infant, or they may cause changes that are detected and presented to the doctor only when the child is older or has even reached adolescence. The range of presentations in relation to the most common causes is summarised in Table 99.4.

Work-up of Infants Born with Ambiguous Genitalia

General Concepts of Care

The consensus conference, comprising members of the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE), highlighted several standards of care recommendations:

Table 99.4: Correlation between mode of clinical presentation and underlying cause.

Mode of presentation	Most common causes
Child with ambiguous genitalia.	• 46,XX DSD due to CAH (21 hydroxylase deficiency) • Sex chromosome DSD (e.g., 45,XO/46,XY partial gonadal dysgenesis and ovotesticular DSD) • 46,XY PAIS • 46,XY 5α-Reductase-2 deficiency • 17β-hydroxysteroid dehydrogenase deficiency
Y(+) girl found to have either testes or dysgenetic gonads.	• 46,XY DSD due to CAIS • 46,XY DSD due to complete gonadal dysgenesis
Adolescent girl with primary amenorrhoea who is found to have no uterus and/or vagina. She may be 46,XX and have ovaries or be 46,XY and have testes.	• 46,XX Müllerian agenesis • 46,XY CAIS
46,XY boy with impalpable or inguinal testes who is found at surgery to have a uterus and fallopian tubes.	• 46,XY persistent Müllerian duct syndrome
Boy with impalpable gonads who is found to have ovaries and a uterus. Or older boy with impalpable gonads who presents with isosexual precocious puberty.	• 46,XX DSD due to CAH (21-hydroxylase deficiency)
Girl who, although born with typical female genitalia, undergoes progressive clitoral enlargement and other signs of virilisation during childhood or adolescence.	• 46,XY DSD due to 17β-hydroxysteroid dehydrogenase deficiency

1. gender assignment for all;

2. avoidance of assignment before expert evaluation;

3. open communication;

4. a multidisciplinary team approach; and

5. confidentiality and attention to patient and family concerns (adolescent patients should be given opportunities to ask questions and discuss their condition confidentially, without their parents being present).

A key point to emphasize is that the child with DSD has the potential to become a well-adjusted, functional member of society. Although privacy needs to be respected, a DSD is not shameful. It should be explained to the parents that the best course of action may not be clear initially, but the health care team will work with the family to reach the best possible set of decisions in the circumstances. The health care team should discuss with the parents what information to share in the early stages with family members and friends. Parents need to be informed about sexual development in a balanced simple way.

The multidisciplinary team

Optimal care for children with DSDs requires an experienced multidisciplinary team generally found in tertiary care centres and ideally including paediatric subspecialists in endocrinology, surgery or urology, psychology or psychiatry, gynecology, genetics, and neonatology. The multidisciplinary team can play a critical role in creating a climate of commitment to the health and welfare of children born with DSDs, as well as to their families.

Clinical evaluation

The evaluation and initial management of the newborn with ambiguous genitalia must be regarded as a medical and psychosocial emergency and be handled with great sensitivity toward the family. In obtaining the history, certain pieces of information may be particularly valuable. A history of infant death within the family might suggest the possibility of CAH, and infertility, amenorrhea, or hirsutism might also suggest possible familial patterns of disorders. Maternal use of medications during the pregnancy, in particular steroids or contraceptives, is of great importance.

The initial physical examination should begin with an assessment of the general health of the patient and an evaluation for malformations or dysmorphic features because ambiguous genitalia can occur in conjunction with several other congenital malformations. It is necessary to look for signs of dehydration with vomiting and diarrhoea because these are symptoms of a salt-losing crisis. A careful examination of the external genitalia must also be performed. A genital exam must include a measure of stretched phallic length, evaluation of the quality of the corpora, and inspection of the labia, labio-scrotal folds, or scrotum. The position of the urethral opening (and vaginal opening, if applicable) should be documented, as well as the presence and location of palpable gonads.

Investigations

Within the immediate newborn period, a karyotype should be obtained. Typically this requires 2–3 days to perform. Serum studies should be immediately sent to rule out a salt-wasting form of CAH. In addition to serum electrolytes, testosterone and DHT should be measured early because their levels may drop quickly. In addition, serum 17-hydroxyprogesterone should not be measured until day 3 or 4 to rule out 21-hydroxylase deficiency because the stress of delivery may result in a physiologic elevation of this steroid precursor in the first 1 or 2 days of life. The suggested schedule for hormone studies in an infant with ambiguous genetalia is as follows:

- At day 2 of life, measure plasma androstenedione, testosterone, and dihydrotestosterone. These androgens must be measured from a single blood sample so that the ratios of androstenedione/testosterone and testosterone/DHT can be calculated.
- At day 3 or 4 of life, measure plasma 17-hydroxyprogesterone, 17-hydroxypregnenolone, and progesterone.
- At day 6 or 7 of life, measure plasma MIS and obtain white cells for deoxyribonucleic acid (DNA) studies, such as androgen receptor gene mutations.
- At day 8 of life, repeat androstenedione, testosterone, DHT, and 17-hydroxyprogesterone measures.

A sonogram or magnetic resonance imaging (MRI) can be helpful in identifying both the type and extent of internal sex organ development. Imaging can also detect associated abnormalities of the urinary tract. Laparotomy or laparoscopy and gonadal biopsy are usually the next definitive clinical step required when a firm diagnosis based on the aforementioned data is impossible. Laparotomy or laparoscopy in this setting remains a diagnostic manoeuvre; removal of gonads or reproductive organs should be deferred until the final pathology report

is available and a gender has been assigned. Detection of AR gene mutations may help, although current molecular diagnosis is limited by cost, accessibility, and quality control.

Finally, anatomic definition of the urogenital sinus and ductal structures contributes to the correct diagnosis and is necessary before any surgical intervention. The urogenital sinus and ductal structures are well imaged by genitogram, which defines the entry of urethra and vagina into the sinus and outlines the cervical impression within the vagina. Endoscopy can define these relationships further, but is usually not necessary until surgical reconstruction becomes imminent.

Gender Assignment

The basis of gender assignment should include:

- The most likely adult gender identity based on impression of foetal androgen exposure, parents' expectations, and expected impact of sexual differentiation;
- diagnosis;
- genital appearance;
- genital surgical options (potential for functional, sensitive genitalia);
- potential for fertility (considering assisted fertility techniques);
- social and cultural pressures; and
- family dynamics (parents' desires, expectations, malleability, and reactions to genital ambiguity).

The relative weight of the gender assignment interrelated factors differ in each situation. The magnitude of the impact of each factor upon the others is also variable over time. Depending on the degree of unpredictability of outcome, deference is given to psychosocial factors.

This approach recognizes the powerful influence of parental input on outcomes. Medical decisions in the DSD patient are usually made in what has been referred to as the category III level of evidence (opinions of respected authorities based on clinical experience, descriptive studies and case reports, or reports of expert committees). Thus, major limitations exist in making recommendations for DSD patients for most issues. Guidelines for gender assignment are addressed only for those DSD patients with substantial outcome data (Table 99.5).

Table 99.5: Current diagnosis-based recommendations for sex of rearing.

Diagnosis	Sex of rearing
46,XY CAIS	Female
46,XY PAIS	Dependent upon judgment of degree of masculinisation and parental input
46,XX CAH	Female, realizing that there are anecdotal reports, but not verified documentation, of those with essentially male external genitalia raised satisfactorily as male
5α-reductase deficiency	Strongly consider male assignment
17β-hydroxysteroid dehydrogenase deficiency	Strongly consider male assignment
Cloacal exstrophy	Conflicting outcome data; reports from the United States show high rates of self-reassignment to male
Ovotesticular DSD	Consider external genital development and fertility potential; given outcome uncertainties, potential for fertility (assuming consistent genitalia) is a major factor

Management of Patients with DSD

The consensus conference recognised the role of various entities in decision making for the DSD child, including the parent, the child, and the medical system. A practical application of these roles and ways to resolve potential conflicts between decision makers were not addressed, however. Decision making should be based on ethical, human rights, and legal grounds. Some important universally applicable ethical principles can be followed, such as minimising physical risk (e.g., malignancy) to the child; minimising psychosocial risk (e.g., social isolation) to the child; preserving potential for fertility; preserving or promoting capacity to have satisfying sexual relations; and leaving options open for the future.

Surgical Management

The surgeon has a responsibility to outline the surgical sequence and subsequent consequences from infancy to adulthood. Only surgeons with expertise in the care of children and specific training in the surgery of DSD should perform these procedures. The consensus, based upon the recommendations of the surgical subgroup, agreed that the primary goal of genital surgery was to improve functional rather than cosmetic outcome to enhance sexual function and romantic partnering.

Rationale for early reconstruction includes the beneficial effects of estrogen on infant tissues, avoiding complications from anatomic anomalies, satisfactory outcomes, minimising family concern and distress, and mitigating the risks of stigmatisation and gender-identity confusion of atypical genital appearance. Adverse outcomes have led to recommendations to delay unnecessary genital surgery to an age of patient-informed consent, although relative risks and benefits are unknown.

Feminising genital surgery involves external genitalia reconstruction and vaginal exteriorisation, with early separation of the vagina and urethra. Clitoral reduction is considered with severe virilisation and performed in conjunction with common urogenital sinus repair. Total urogenital mobilisation and clitoplasty is the procedure of choice in the authors' unit and is done in infancy starting from 6 months of age (Figure 99.5). Long-term follow-up of more than 50 cases reveals a very good cosmetic outcome, no urinary sequel, and very few complications (Figure 99.6).

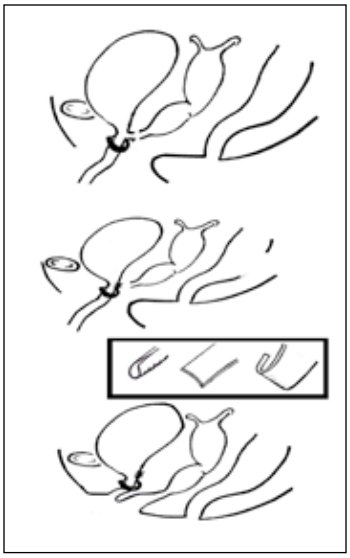

Figure 99.5: Total urogenital sinus mobilisation.

Figure 99.6: Postoperative view.

Vaginal dilatation should not be performed during childhood. Refinement is sometimes necessary at puberty for other procedures. Surgery should emphasize functional cosmetic appearance and be designed to preserve erectile function and innervation. Substitution vaginoplasty should be performed in the teenage years; each of the techniques (self-dilatation, skin or bowel substitution) has specific advantages and disadvantages, and all carry potential for scarring that would require modification before sexual function.

Masculinising genital surgery involves more surgical procedures and urologic difficulties than feminising genitoplasty. Standard surgical repair involving hypospadias includes chordee correction, urethral reconstruction, and judicious testosterone supplementation. If needed, adult-sized testicular prostheses should be inserted after sufficient pubertal scrotal development. The enormity of the undertaking and complexity of phalloplasty must be considered during the initial counselling period. Care should be taken to avoid unrealistic expectations about penile reconstruction.

Gonadectomy is indicated in patients at high risk of developing germ cell malignancy. The highest tumour risk is found in testis-specific protein Y (TSPY)-encoded positive gonadal dysgenesis and PAIS with intraabdominal gonads, whereas the lowest risk (<5%) is found in ovotestis and CAIS. Specifically:

- For patients with CAIS or PAIS raised female, the testes should be removed to prevent malignancy in adulthood. The availability of estrogen-replacement therapy allows for the option of early removal at the time of diagnosis.
- The streak gonad in patients with MGD raised male should be removed laparoscopically (or by laparotomy) in early childhood. Bilateral gonadectomy is performed in early childhood in females (bilateral streak gonads) with gonadal dysgenesis and Y-chromosome material.
- For patients with androgen biosynthetic defects raised female, gonadectomy should be performed before puberty.
- A scrotal testis in patients with gonadal dysgenesis is at risk for malignancy. Current recommendations are testicular biopsy at puberty, seeking signs of the premalignant lesion termed carcinoma in situ or undifferentiated intratubular germ cell neoplasia. If positive, the option is sperm banking before treatment with local low-dose radiotherapy that is curative.

Sex-Steroid Replacement

Hormonal induction of puberty stimulates replication of normal pubertal maturation to induce secondary sexual characteristics, a pubertal growth spurt, and optimal bone mineral accumulation, together with psychosocial support for psychosexual maturation. Intramuscular depot injections of testosterone esters are commonly used in males; another option is oral testosterone. Transdermal preparations are also available. Patients with PAIS may require supraphysiologic doses of testosterone for optimal effect. Females with hypogonadism require estrogen supplementation to induce pubertal changes and menses. A progestin is usually added after breakthrough bleeding develops or within 1–2 years of continuous estrogen. There is no evidence that the addition of cyclic progesterone is beneficial in women without a uterus.

Lifelong glucocorticoid replacement therapy is the mainstay of treatment for classic and symptomatic nonclassic CAH patients. Glucocorticoids not only replace cortisol but also reduce the overstimulation of the adrenal cortex by reducing the release of ACTH, thereby suppressing the overproduction of adrenal androgens. Hydrocortisone is usually chosen for infants and children, as it is shorter acting than prednisone or dexamethasone, and thus less likely to compromise growth. Excessive glucocorticoid administration should be avoided because it can cause Cushingoid facies, growth retardation, and inhibition of epiphyseal maturation. Patients with salt-wasting CAH may also require mineralocorticoid replacement.

Psychosocial Management

Psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management to promote positive adaptation. This expertise can facilitate team decisions about gender assignment/reassignment, timing of surgery, and sex-hormone replacement. Gender identity (a personal concept of oneself as male or female, or, rarely, both or neither) development begins before the age of 3 years, but the earliest age at which it can be reliably assessed remains unclear. The generalisation that the age of 18 months is the upper limit of imposed gender reassignment should be treated with caution and viewed conservatively. Atypical gender-role behavior (the outward manifestations of personality that reflect the gender identity) is more common in children with DSD than in the general population, but should not be taken as an indicator for gender reassignment. In affected children and adolescents who report significant gender dysphoria, a comprehensive psychological evaluation and an opportunity to explore feelings about gender with a qualified clinician are required over a period of time. If the desire to change gender persists, the patient's wishes should be supported.

The process of disclosure of all aspects of the DSD and its clinical care should be collaborative, ongoing, and planned with the parents from the time of diagnosis. Medical education and counselling are recurrent gradual processes of increasing sophistication that take into account the patient's changing cognitive and psychological development. Quality of life encompasses dating, falling in love, ability to develop intimate relationships, sexual functioning, and the opportunity to marry and to raise children, regardless of biological indicators of sex. Because of fears of rejection in intimate relationships, a focus of psychological care should be interpersonal relationships. Frequent problems encountered in patients with DSD are sexual aversion and lack of arousability, often misinterpreted as low libido. Repeated examination of the genitalia, including medical photography, may be experienced as shaming and should be undertaken when the patient is under anaesthesia whenever possible.

Outcomes

As a general statement, information across a range of assessments is insufficient in DSD. With regard to surgical outcome, some studies suggest satisfactory outcomes from early surgery; however, other studies on clitoroplasty identify problems related to decreased sexual sensitivity, loss of clitoral tissue, and cosmetic issues. Interpretation of published reports on the risk of gonadal tumours is hampered by unclear terminology and by the effects of normal cell maturation delay.

Concerning cultural and social factors, DSD may carry a stigma. Gender role change occurs at different rates in different societies, suggesting that social factors may also be important modifiers of gender role change. In the West, when selection of the optimal gender is being considered, a great deal of attention will be paid to whether the child will grow up able to enjoy sexual pleasure and fulfillment. Eastern thinking, in contrast, is more concerned with ensuring that the individual (especially if brought up as a girl) will be capable of having sexual intercourse to satisfy a partner.

In some societies, female infertility precludes marriage, which also affects employment prospects and creates economic dependence. Religious and philosophical views may influence the parents' response to the birth of an infant with a medical condition. Poverty and illiteracy negatively affect access to health care.

Evidence-Based Research

The impact of reduction of the enlarged clitoris on adult sexuality has not been sufficiently evaluated in CAH or other DSDs. Follow-up studies in childhood have not been able to assess sexual function. A few previous reports considered surgical outcomes but they were small case series, and methodical assessment of genital sensitivity and sexual function were not performed. Table 99.6 presents a study of genital sensitivity following feminising genitoplasty for CAH.

Table 99.6: Evidence-based research.

Title	Sexual function and genital sensitivity following feminizing genitoplasty for congenital adrenal hyperplasia
Authors	Crouch NS, Liao LM, Woodhouse CRJ, Conway GS Creighton SM
Institution	The Middlesex Centre, University College London, Institute of Women's Health, Elizabeth Garrett Anderson and Obstetric Hospital, and Institute of Urology, University College London Hospital (CRJW), London, UK
Reference	J Urol 2008; 179:634–638
Problem	Evaluation of the effect of feminising genital surgery on genital sensation and sexual function in women with CAH.
Intervention	Sensitivity thresholds for temperature and vibration for the clitoris and upper vagina were measured by using a GenitoSensory Analyzer. Sexual function was assessed by using a mailed questionnaire incorporating the Golombok Rust Inventory of Sexual Satisfaction.
Comparison/ control (quality of evidence)	This was a cross-sectional study of genital sensitivity in 28 women with CAH, 17 to 39 years old (mean age, 25.4); and 10 normal controls, 23 to 38 years old (mean age, 25.3). Four women with CAH had not undergone prior genital surgery. None of the normal controls was known to have any endocrine abnormality or history of genital surgery. The study consisted of two parts: (1) sensitivity testing of the clitoris and upper vagina, and (2) completion of a mailed sexual function questionnaire.
Outcome/ effect	Sensitivity is decreased in genital areas where feminising genitoplasty has been done. Surgery is also associated with sexual difficulties. A moderate but significant linear relationship between impaired clitoral sensitivity and the severity of sexual difficulties has been identified.
Historical significance/ comments	1. All patients in this study underwent their surgical correction in the early 1980s. The results of this study cannot be generally applied to current patients. Today, the neuroanatomy of the clitoris is better understood than it was 25 or more years ago, and current techniques give more concern to preserve the neurovascular bundle of the clitoris, so the clitoral sensation is much less affected. 2. If possible, no clitoral surgery should be performed, as no evidence suggests that a large clitoris is detrimental to sexual function. However, in most cases, the clitoris is quite large, appearing like a penis. In such cases clitoral reduction should be discussed with the parents after detailed consent. 3. The sexual function assessment in this study was dependent on a subjective method (a mailed questionnaire). The answers, and hence the final assessment, will be greatly affected by cultural and behavioural factors. Eastern thinking is more concerned with ensuring that the female will be capable of having sexual intercourse to satisfy her partner. In contrast, in the West, great concern is paid to whether the child will grow up able to enjoy sexual pleasure and fulfillment. 4. A large cohort of studies, in addition to accurate objective measures, are needed to justify the final outcome of feminising surgery, and hence outline the guidelines more precisely.

Key Summary Points

1. Disorders of sex development (DSD) is new terminology that replaces the well-known terminology "intersex".
2. DSD is a congenital condition characterised by atypical development of chromosomal, gonadal, or anatomical sex.
3. DSD is classified as sex chromosome DSD, 46,XY DSD, and 46,XX DSD.
4. Management of infants suffering from DSD is challenging, especially in Africa and developing countries due to educational, financial, and behavioural factors.
5. Cases should be managed through a multidisciplinary team.
6. No assignment should be offered before full work-up, and reassignment should be considered in some cases.
7. Surgical correction should be based on anatomical and functional bases rather than a cosmetic one, although the importance of cosmesis should not be ignored.
8. Early correction is advised in congenital adrenal hyperplasia; otherwise, delay of surgery is advisable in most cases.
9. Gonadectomy should be performed in cases at high risk to develop gonadal carcinoma as well as in cases suffering gonadal dysgenesis or PAIS with intraabdominal gonads.

Suggested Reading

American Academy of Pediatrics, Committee on Genetics. Evaluation of the newborn with developmental anomalies of the external genitalia. Pediatrics 2000; 106:138–142.

American Academy of Pediatrics, Section on Urology. Timing of elective surgery on the genitalia of male children with particular reference to the risks, benefits, and psychological effects of surgery and anesthesia. Pediatrics 1996; 97:590–594.

Cohen-Kettenis P. Psychological long-term outcome in intersex conditions, Horm Res 2005; 64:27–30.

Crouch NS, Minto CL, Laio LM, Woodhouse CR, Creighton SM. Genital sensation after feminizing genitoplasty for congenital adrenal hyperplasia: a pilot study. BJU Int 2004; 93:135–138.

Diamond DA. Sexual differentiation: normal and abnormal. In: Wein AJ (ed). Campbell-Walsh Urology, Saunders, Elsevier, 2007, Pp 3799–3829.

Dreger AD, Chase C, Sousa A, Grupposo PA, Frader J. Changing the nomenclature/taxonomy for intersex: a scientific and clinical rationale. J Pediatr Endocrinol Metab 2005; 18:729–733.

Eroğlu E, Tekant G, Gündoğdu G, et al. Feminizing surgical management of intersex patients. Pediatr Surg Int 2004; 20:543–547.

Hamza AF, Soliman HA, Abdel Hay SA, Kabesh AA, Elbehery MM. Total urogenital sinus mobilization in the repair of complex female genital anomalies. J Pediatr Surg 2001; 36:1656–1668.

Houk CP, Lee PA. Disorders of sex development: making ambiguity less ambiguous. Growth, GeneticHormones J 2007; 23:33–39.

Houk CP, Hughes IA, Ahmed SF, Lee PA, Writing Committee for the International Intersex Consensus Conference. Summary of consensus statement on intersex disorders and their management. Pediatrics 2006; 118:753–757.

Intersex Society of North America. Clinical guidelines for the management of disorders of sex development in childhood, Consortium on the Management of Disorders of Sex Development. Available at www.dsdguidelines.org/htdocs/clinical/index.html (accessed 2006).

Kuhnle U, Krahl W. The impact of culture on sex assignment and gender development in intersex patients. Perspect Biol Med 2002; 45:85–103.

Lee PA, Houk CP, Ahmed SF, Hughes IA, in collaboration with the participants in the International Intersex Consensus Conference. Consensus statement on management of intersex disorders, 2006, 118:e488–e500.

Maharaj N, Dhai A, Wiersma R, Moodley J. Intersex conditions in children and adolescents: surgical, ethical, and legal considerations. J Pediatr Adolesc Gynecol 2005; 18:399–402.

Martin CL, Ruble DN, Szkrybalo J. Cognitive theories of early gender development. Psychol Bull 2002; 128:903–933.

Merke D, Cutler G. New ideas for medical treatment of congenital adrenal hyperplasia. Endocrinol Metab Clin North Am 2001; 30:121–135.

Migeon CJ, Krishnan S, Wisniewski AB. Ambiguous genitalia in the newborn. Available at http:www.endotext.org/pediatrics/pediatrics10/pediatricsframe10.htm (accessed 2007).

Mouriquand PD, Mure PY. Current concepts in hypospadiology. BJU Int 2004; 93:26–34.

New MI, 21-hydroxylase deficiency: classical and nonclassical congenital adrenal hyperplasia. Available at: http://www.endotext.org/pediatrics/pediatrics8a/pediatricsframe8a.htm (accessed 2006).

Warne GL, Raza J. Disorders of sex development (DSDs), their presentation and management in different cultures. Rev Endocr Metab Disord 2008; 9:227–236.

Warne GL, Grover S, Zajac JD. Hormonal therapies for individuals with intersex conditions: protocol for use. Treat Endocrinol 2005; 4:19–29.

Wisniewski AB, Migeon CJ, Meyer-Bahlburg HF, et al. Complete androgen insensitivity syndrome: long-term medical, surgical and psychosexual outcome, J Clin Endocrinol Metab 2000; 85:2664–2669.