Early assessment of ambiguous genitalia

A L Ogilvy-Stuart and C E Brain

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Determination of sex

Early assessment of ambiguous genitalia

A L Ogilvy-Stuart, C E Brain

A multidisciplinary problem

To discover that there is uncertainty about the sex of one's newborn baby is devastating and often incomprehensible for most parents. It is paramount that clear explanations and investigations are commenced promptly, and that no attempt is made to guess the sex of the baby. Extreme sensitivity is required, and ideally the baby should be managed in a tertiary centre by a multidisciplinary team including a specialist laboratory facilities and a paediatric urologist. Early involvement of a clinical psychologist with experience in this field should be mandatory. Other professionals including geneticists and gynaecologists may also become involved. There must be access to specialist laboratory facilities and experienced radiologists. The incidence of genital ambiguity that results in the baby's sex being uncertain is 1 in 4500, although some degree of male undervirilisation, or female virilisation may be present in as many as 2% of live births.

Parents require reassurance that either a male or female gender will definitely be assigned. However the outcome of some of the investigations may take some weeks, and registration of the child's birth should be deferred until gender has been assigned. This may require communication with the Registrar of Births, and a skilled clinical psychologist will help the parents in deciding what to tell family and friends in the interim. It is also helpful (if appropriate) to reassure the parents that their child is otherwise healthy.

While not all intersex conditions are apparent at birth (for example, complete androgen insensitivity may only become apparent in a child with a testis within an inguinal hernia, or at puberty with primary amenorrhoea and lack of androgen hair), only those presenting with genital ambiguity at birth will be considered in this article.

An understanding of sex determination and differentiation is essential to direct appropriate investigations and to establish a diagnosis.

Genetic sex is determined from the moment of conception and determines the differentiation of the gonad. The differentiation of the gonad in turn determines the development of both the internal genital tracts and the external genitalia and thus phenotypic sex, which occurs later in development (from about 5–6 weeks of gestation). Both male and female genitalia differentiate from the same structures along the urogenital ridge. At about 4 weeks after fertilisation, primordial germ cells migrate from the yolk sac wall to the urogenital ridge that develops from the mesonephros. The urogenital ridge also contains the cells that are the precursors for follicular or Sertoli cells and steroid producing theca and Leydig cells. The "indifferent" gonads form on the genitopelvic ridge.

The development of the fetal adrenals and gonads occur in parallel, as before migration, the potential steroidogenic cells of both originate from the mesonephros. There are many genes and transcription factors that are expressed in both tissues (for example, SF1 and DAX1), and hence mutations in these genes may affect both adrenal and gonadal development (fig 1). In addition, WT1 is expressed in the kidney and gonad, hence the association of Wilms' tumour and gonadal dysgenesis in Denys-Drash syndrome, for example.

The undifferentiated gonad is capable of developing into either an ovary or a testis. The theory that the "default" programme generates an ovary is probably not correct, although the exact role of "ovarian determining" genes in humans is unclear at present. In contrast, testicular development is an active process, requiring expression of the primary testis determining gene SRY, and other testis forming genes such as SOX9. Transcription factors such as SF1 and WT1 are also required for development of the undifferentiated gonad, as well as for the activation of the other male pathway genes required for testis development and the consequent development of male internal and external genitalia.

DAX1 and Wnt4 are two genes that may act to "antagonise" testis development. Over-expression of DAX1 (through duplication of Xp21) and Wnt4 (through duplication of 1p35), have been associated with impaired gonadal development and undervirilisation in a small number of karyotypic 46 XY males.

Mutations or duplications in the various genes responsible for gonadal differentiation and the subsequent development of the internal and external genital phenotype genes may be responsible for gonadal dysgenesis and in some cases complete sex reversal (table 1).

Wnt4 is also expressed in the Müllerian ducts and in the absence of anti-Mullerian hormone (AMH) (also known as Mullerian inhibiting substance) and testosterone, Müllerian structures develop, while the Wolffian ducts involute. AMH promotes regression of Müllerian structures and as the only source of AMH in the fetus is the testes, the absence of a uterus in a baby with ambiguous genitalia is evidence that there has been functional testicular tissue (Sertoli cell) present. Testosterone produced from Leydig cells promotes differentiation of the Wolffian ducts and hence the internal male genitalia (vas deferens, epididymis, and seminal vesicles).

Testosterone is converted to dihydrotestosterone [DHT] by the enzyme 5α-reductase. DHT masculinises the external genitalia from about 6 weeks gestation, and the degree of masculinisation is determined by the amount of fetal androgen present (irrespective of source) and the ability of the tissues to respond to the androgens.

Defects in any part of this pathway (including genes mutations and chromosomal abnormalities (for example, 46XY/46XX, 45X/46XY), inappropriate hormone levels, or end-organ unresponsiveness) may result in genital ambiguity, with undervirilisation of an XY individual, virilisation of an XX individual, or the very rare true hermaphrodite (an individual with both ovarian tissue with primary follicles and testicular tissue with seminiferous tubules which may be in separate gonads or ovotestes).

CLINICAL ASSESSMENT OF AMBIGUOUS GENITALIA

History
The history should include details of the pregnancy, in particular the use of any.

Abbreviations: AMH, anti-Mullerian hormone; CAH, congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; DHT, dihydrotestosterone; EUA, examination under anaesthesia; HCG, human chorionic gonadotrophin; STAR, steroidogenic acute regulatory protein.
drugs (table 2) that may cause virilisation of a female fetus and details of any previous neonatal deaths (which might point to an undiagnosed adrenal crisis). A history of maternal virilisation may suggest a maternal androgen secreting tumour or aromatase deficiency. A detailed family history should be taken, including whether the parents are consanguineous (which would increase the probability of an autosomal recessive condition) or if there is a history of genital ambiguity in other family members (for example, an X-linked recessive condition such as androgen insensitivity).

Examination

The general physical examination should determine whether there are any dysmorphic features and the general health of the baby. A number of syndromes are associated with ambiguous genitalia, for example, Smith-Lemli-Opitz syndrome (characterised by hypocholesterolaemia and elevated 7-dehydrocholesterol levels, and resulting from mutations affecting 7-dehydrocholesterol reductase), Robinow syndrome, Denys-Drash syndrome, and Beckwith-Wiedemann syndrome. Midline defects may point towards a hypothalamic-pituitary cause for microgenitalia and cryptorchidism. Hypoglycaemia may indicate cortisol deficiency secondary to hypothalamic-pituitary or adrenocortical insufficiency.

The state of hydration and blood pressure should be assessed as various forms of congenital adrenal hyperplasia (CAH) can be associated with differing degrees of salt loss, varying degrees of virilisation in girls or undervirilisation in boys.

Figure 1  Normal sexual differentiation. SRY, sex determining region on Y chromosome; TDF, testis determining factor; AMH, anti-Mülllerian hormone; T, testosterone; DHT, dihydrotestosterone; WT1, Wilms tumour suppressor gene; SF1, steroidogenic factor 1, SOX9, SRY-like HMG-box; Wnt4, Wnt—a group of secreted signalling molecules that regulate cell to cell interactions during embryogenesis; DAX1, DSS-AHC critical region on the X chromosome.

Table 1  Consequences of mutations/deletions and duplications/translocations of genes involved in gonadal differentiation

<table>
<thead>
<tr>
<th>Chromosome location</th>
<th>Gonadal development</th>
<th>Associated disorder</th>
<th>Sex reversal/genital ambiguity</th>
<th>Müllerian development</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT1 11p13</td>
<td>Dysgenesis (♂ and ♀)</td>
<td>WAGR syndrome</td>
<td>Genital ambiguity (♂)</td>
<td>Variable (♂)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Denys-Drash syndrome</td>
<td>Sex reversal or genital</td>
<td>Variable (♂)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adrenal failure</td>
<td>ambiguity (♂)</td>
<td></td>
</tr>
<tr>
<td>SF1 9q33</td>
<td>Dysgenesis (♂)</td>
<td>Frasier syndrome</td>
<td>Sex reversal (♂)</td>
<td>Yes (♂)</td>
</tr>
<tr>
<td>SRY Yp11.3</td>
<td>♂—♀ ovary</td>
<td>Adrenal failure and</td>
<td>Sex reversal or genital</td>
<td>Yes (♂)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypogonadotrophic</td>
<td>ambiguity (♂)</td>
<td></td>
</tr>
<tr>
<td>DAX1 Xp21</td>
<td>Dysgenesis</td>
<td>Adrenal failure and</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypogonadal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOX9 17q24.3–25.1</td>
<td>Dysgenesis or</td>
<td>Campomelic dysplasia</td>
<td>Sex reversal or genital</td>
<td>Variable</td>
</tr>
<tr>
<td>AMH 19p 13.3–13.2</td>
<td>ovary/ovotestis</td>
<td></td>
<td>ambiguity (♂)</td>
<td></td>
</tr>
<tr>
<td>SRY Y fragment</td>
<td>Testis</td>
<td></td>
<td>Sex reversal or genital</td>
<td>No</td>
</tr>
<tr>
<td>DAX1 duplication</td>
<td>dupXp21</td>
<td></td>
<td>Sex reversal or genital</td>
<td>Variable</td>
</tr>
<tr>
<td>Wnt 4 duplication</td>
<td>dupYp25</td>
<td></td>
<td>Genital ambiguity (♂)</td>
<td>Yes</td>
</tr>
<tr>
<td>SOX9 duplication</td>
<td>dup1/p24.3–25.1</td>
<td></td>
<td>Genital ambiguity (♂)</td>
<td>No</td>
</tr>
</tbody>
</table>

WAGR, Wilms’ tumour, aniridia, genitourinary anomalies, mental retardation; Denys-Drash (exonic mutations) WT, diffuse mesangial sclerosis; Frasier (intrinsic mutations) no WT, focal segmental glomerulosclerosis. Other abbreviations as for fig 1.
down into the labial scrotal folds may be normal or dysgenetic. Flat finger likely to be testes (or ovotestes) which hypospadias (stage V) (fig 2). to a phenotypic male with glandular female with mild cliteromegaly (stage I) increasing virilisation from a phenotypic stages). Examination of the external genitalia and Prader staging Examination of external genitalia and Prader staging Examination of the external genitalia determines whether gonads are palpable and the degree of virilisation or Prader stage. Prader stages I–V describe increasing virilisation from a phenotypic female with mild cliteromegaly (stage I) to a phenotypic male with glandular hypospadias (stage V) (fig 2). If both gonads are palpable they are likely to be testes (or ovotestes) which may be normal or dysgenetic. Flat finger palpation from the internal ring milking down into the labial scrotal folds may detect the presence of a gonad. They may be situated high in the inguinal canal so careful examination is required. A unilateral palpable gonad may be a testis, ovotestis, or rarely an ovary within an inguinal hernia. Congenital adrenal hyperplasia must be excluded in a phenotypically male baby with bilateral undescended testes.

The length of the phallus should be determined. The normal term newborn penis is about 3 cm (stretched length from pubic tubercle to tip of penis) with micropenis less than 2.0–2.5 cm, although this does vary slightly depending on ethnic origin. Chordee should be noted as this may decrease the apparent length of the phallus and the penis may be ‘‘buried’’ in some cases. The presence of hypospadias and the position of the urethral meatus should be determined. The urine may be coming from more than one orifice. The degree of fusion and rugosity of the labioscrotal folds should be noted and the presence or absence of a separate vaginal opening determined.

Hyperpigmentation, especially of the genital skin and nipples occurs in the presence of excessive ACTH and proopiomelanocortin and may be apparent in babies with CAH. The gestation of the baby can cause confusion—in preterm girls the clitoris and labia minora are relatively prominent and in boys, the testes are usually undescended until about 34 weeks gestation.

INVESTIGATIONS

Initial investigations ascertain whether the child is an undervirilised male or a virilised female and from these a differential diagnosis can be established and subsequent investigations planned (fig 3). The principal aims of the initial investigations are to determine the most appropriate sex of rearing and in a genetic female, to exclude CAH and avert a salt losing crisis. Rarer forms of CAH (steroidogenic acute regulatory protein (STAR) deficiency, 3β-hydroxysteroid dehydrogenase deficiency) may also present with an adrenal crisis in undervirilised males.

Karyotype As the differential diagnosis and a number of subsequent investigations will depend on the genetic sex, an urgent karyotype should be sent. Rapid FISH studies using probes specific for the X (DX1) and Y (SRY) chromosomes can provide useful information, although a full karyotype is required for confirmation and exclusion of mosaicism. The latter may be tissue specific and may not be apparent from blood, but only from skin or gonadal biopsies. In cases with a mosaic karyotype, for example, XO/XY or XX/XY, the gonads are often different. This may involve one being a streak gonad and the other a testis or ovotestis, or two ovotestes with different ovarian and testicular components.

Determination of internal anatomy As with the external genitalia, the degree of virilisation of the internal genital tracts is defined by Prader stages I–V (fig 2). The anatomy of the vagina or a urogenital sinus and uterus may be determined by ultrasound, and if necessary, further delineation by EUA/cystoscopy or urogenital sinogram. Ultrasound is also useful in excluding associated renal anomalies, particularly if Denys-Drash syndrome is suspected or proven. It may also be used to visualise the adrenal glands. Ultrasound may also locate inguinal gonads, although it is not sensitive for intra-abdominal gonads. Ultrasound sensitivity and accuracy depend on probe resolution; an experienced ultrasonographer is required. Identification of the gonads may require magnetic resonance imaging (MRI) or laparoscopy. These latter investigations are also useful for determining the anatomy of the internal
Differential virilisation of the external genitalia using the staging system of Prader, from the gonad is normally most active between performing the hCG test when reaching a peak at about 6–8 weeks of any time in childhood until puberty, 24 hours after the last injection. The samples are taken at 72 hours or dose hCG (500–1500 IU) are given at three intramuscular injections of high dione and its metabolite (DHT). One to sulphate (DHEAS)) and androstene-dione (DHEA (or DHEA testosterone to DHT (5 α-hydroxysteroid dehydrogenase deficiency) or conversion of testosterone to DHT (5 α-reductase deficiency). There are a variety of protocols for the hCG test, but essentially it involves taking baseline samples androstenedione (17β)-hydroxysteroid dehydrogenase deficiency) or conversion of testosterone to DHT (5α-reductase deficiency). There are a variety of protocols for the hCG test, but essentially it involves taking baseline samples for testosterone and its precursors dehydroepiandrosterone (DHEA) (or DHEA sulphate (DHEAS)) and androstenedione and its metabolite (DHT). One to three intramuscular injections of high dose hCG (500–1500 IU) are given at 24 hour intervals and repeat androgen samples are taken at 72 hours or 24 hours after the last injection. The neonatal gonad is more active than at any time in childhood until puberty, reaching a peak at about 6–8 weeks of age. A balance needs to be reached between performing the hCG test when the gonad is normally most active (testosterone secretion normally rises in the fourth week of life, peaking at 1–3 months) and proceeding with the investigations as promptly as possible. While some would advocate that this test is deferred beyond 2 weeks of age, this may not be necessary. In the newborn period an increase in testosterone, reaching adult male levels, would normally be expected after hCG.

The hCG test can be extended to a three week test if the three day hCG test is inconclusive. The same dose of hCG is administered twice weekly for three weeks and testosterone, DHT, and androstenedione samples taken 24 hours after the last hCG injection. The clinical response in terms of testicular descent and change in the size of the phallus and frequency of erections should be documented. Photographs pre- and post-hCG, may be helpful.

**Anti-Müllerian hormone (AMH) and inhibin B levels**

While hCG stimulation tests the function of the Leydig cells, both AMH and inhibin B are secreted by the Sertoli cells. Inhibin B is detectable for the first six months, rising again at puberty. AMH levels are high in human male serum postnatally for several years before declining during the peripubertal period, but AMH is undetectable in female serum until the onset of puberty. AMH may prove to be a more sensitive marker for the presence of testicular tissue than serum testosterone levels, both before and after the neonatal androgen surge, and, consequently, may obviate the need for hCG stimulation in the evaluation of certain intersex disorders. Similarly, basal inhibin B has been shown to predict the testosterone response to hCG in boys, and therefore may give reliable information about both the presence and function of the tests. Furthermore, inhibin B levels have been shown to demonstrate specific alterations in patients with genital ambiguity which may aid the differential diagnosis of male undervirilisation.

**Assessment of gonadotrophins**

Assessment of the gonadotrophins may give useful information. Raised basal gonadotrophins are consistent with primary gonadal failure. The gonadotrophin response to GnRH is difficult to interpret in the prepubertal child unless exaggerated, which is consistent with gonadal failure but adds little to the basal levels alone. Pituitary failure would give a flat response but is not diagnostic, and hypothalamic abnormalities such as Kallmann’s syndrome are not excluded by a “normal” response. The optimal time to assess this is within the first six months of life when there is a gonadal surge in both sexes (girls greater than boys), and the axis is hence maximally responsive.

**Assessment of adrenal function**

**Urinary steroid profile**

Output of adrenal steroids will be low in adrenal insufficiency. In CAH specific ratios of metabolites will be altered, depending on the level of the enzyme block.

**Synacthen test**

A standard short Synacthen test is useful in the following situations:

- Suspected CAH where a peak 17α-hydroxypregesterone (17-OHP) of 100–200 nmol/l is suggestive of 21-hydroxylase deficiency. (Higher reference ranges for preterm infants.)
- Suspected CAH to assess adrenal cortical reserve (measurement of cortisol levels).

The dose of Synacthen is dependent on local protocol (example 36 μg/kg or a standard dose of 62.5 μg intravenously or intramuscularly). Cortisol and 17-OHP levels are normally measured at 0 and 30 minutes only as the 60 minute period.
value does not usually contribute further. A normal basal value, or even a normal stimulated response does not exclude the evolution of adrenal insufficiency, and may need to be repeated depending on clinical suspicion. A basal ACTH level may be helpful, but in most laboratories the turnaround time is slower than for cortisol.

**Skin and gonadal biopsies**

Genital skin biopsies (2–4 mm) performed at the time of examination under anaesthesia (EUA) or genitoplasty are useful to establish cell lines for androgen receptor binding assays and analysis of 5α-reductase activity. The cell line is also a source of genomic DNA and RNA and/or subsequent molecular and functional studies. Karyotype analysis for the presence of mosaicism may be indicated. Gonadal biopsies are essential when considering diagnostic categories such as dysgenesis and true hermaphroditism. A detailed histopathological report is essential. As special treatment of the samples may be required, prior discussion with the pathologist or genetics laboratory should take place.

**INTERPRETATION OF RESULTS**

**Genital ambiguity with a 46XX karyotype indicates a virilised female**

The female fetus with ovaries and normal internal genitalia has been exposed to excessive testosterone, and hence dihydrotestosterone (by conversion of testosterone by 5α-reductase) which virilises the external genitalia. The androgens may be derived from the fetal adrenal gland (CAH and placental aromatase deficiency), fetal gonad (the testis or ovotestis in true hermaphroditism), or rarely, exogenously via transplacental passage from the mother (adrenal or ovarian tumours).

Absence of palpable gonads in association with otherwise apparently male genitalia should always alert one to the possibility of a virilised female. By far the commonest cause of this is CAH. Of the enzyme defects that cause virilisation in female fetuses, 21-hydroxylase deficiency is the most frequent (accounting for 90–95%, UK incidence 1/15–20 000). Diagnosis is made on a raised serum 17-hydroxyprogesterone level. This level may be increased in the first 48 hours in normal babies, and may be significantly increased in sick and preterm babies in the absence of CAH. The other enzyme defects that can cause virilisation of female fetuses are 11β-hydroxylase deficiency (where the 11-deoxycortisol levels will be increased) and less commonly 3β-hydroxysteroid dehydrogenase deficiency (diagnosed by raised 17-hydroxyprogrenalone and dehydroepiandrosterone) (table 3).

If CAH is confirmed, the electrolytes need to be watched closely as salt wasting occurs in 70% of cases of 21-hydroxylase deficiency, usually between days 4 and 15. Mineralocorticoid deficiency induces a rise in serum potassium levels (usually the first sign of salt wasting) and sodium levels fall. Urinary sodium levels will be inappropriately high. Further confirmatory tests for CAH are DHEA, androstenedione, testosterone, ACTH, and plasma renin activity, all of which may be increased. From day 3 of life, the ratio of urinary steroid metabolites will be altered depending on the site of the block, and is very helpful in the diagnosis of 21-OHD and the rarer forms of CAH. A skilled ultrasound examination will show normal internal genitalia, but an EUA may be required to confirm the presence of normal Müllerian structures, and to show the level of entry of the vagina into the urogenital sinus, in the case of a single perineal opening.

The excessive androgen may be gonadal in origin—usually from an ovotestis or testis in a true hermaphrodite. While the commonest karyotype of the true hermaphrodite is 46XX (70.6%), the next commonest karyotype is a chromosomal mosaicism containing a Y chromosome (usually 46XX/46XY) (20.2%). It is important to check fibroblast and/or gonadal genotype in these babies, which may contain a mosaic cell line.

Transplacental transfer of androgen may rarely occur if the mother has an androgen secreting tumour (she may be virilised as a result) or from drugs given during pregnancy. Placental aromatase deficiency, by inhibiting the conversion of androgens to oestrogens, may cause virilisation of a female fetus, and in addition, maternal virilisation occurs from placentation of the excessive fetal androgens.

**Table 2** lists conditions that cause virilisation of a female fetus.

**Genital ambiguity with a 46XY karyotype indicates an undervirilised male**

This is a genetically XY male with two testes, but whose genital tract fails to differentiate normally. There are numerous presentations of genital anomaly, from apparently normal female (Prader I) with a palpable gonad through to an apparently normal male with hypospadias (Prader V).

The three main diagnostic categories are: testicular dysgenesis/malfunction, a biosynthetic defect, and end-organ unresponsiveness (table 2).

If the gonads are palpable, they are likely to be testes (or rarely ovotestes). Investigations are directed at determining the anatomy of the internal genitalia, and establishing whether the testicular tissue is capable of producing androgens. Investigations that may help with the former include pelvic ultrasound, examination under anaesthetic with cystoscopy and laparoscopy. Genital skin biopsy specimens can be taken at the time of endoscopies. Occasionally urogenital sinusogram or
MRI can be helpful. Laparoscopy/laparotomy and gonadal biopsy may be required.

Testicular dysgenesis/malfunction A 46 XY karyotype, with low basal and hCG stimulated testosterone and low testosterone precursors suggests either gonadal dysgenesis (which may require laparoscopy and testicular biopsy) or lipoid CAH (caused by an abnormality in the steroidogenic acute regulatory (STAR) protein).

In the latter condition total adrenal failure is confirmed on Synacthen test, electrolytes, and urinary steroids. Because of the other associated gene defects (table 1), there may be other anomalies such as bony dysplasias or renal anomalies, which should be looked for.

The poorly functioning testicular tissue is likely to give a subnormal testosterone response to hCG and basal gonadotrophins will usually be increased, consistent with primary gonadal failure. In addition, the dysgenetic testes may secrete inadequate amounts of anti-Müllerian hormone, and Müllerian structures may be present (although often hypoplastic) in children with gonadal dysgenesis and a 46XY karyotype.

A mosaic karyotype, for example 45X/46XY suggests gonadal dysgenesis. There is a very variable phenotype both in terms of internal and external genitalia, which is not dependent on the percentage of each karyotype as determined by lymphocyte analysis. Over 90% of individuals with prenatally diagnosed 45X/46XY karyotype have a normal male phenotype, suggesting most individuals with this karyotype escape detection and that an ascertainment bias exists towards those with clinically evident abnormalities.13 14

Biosynthetic defect A 46XY karyotype, low basal and peak testosterone level on hCG testing, often with increased gonadotrophins suggests a diagnosis of an inactivating mutation of the LH receptor (Leydig cell hypoplasia). This condition is associated with a variable phenotype from a completely phenotypic female to undervirilisation of varying degrees.15

A 46XY karyotype with normal or increased basal and peak testosterone on hCG test, and an increased T:DHT ratio is seen in 5a-reductase deficiency. DHT dependent virilisation of external genitalia is deficient, resulting in a small phallus and perineal hypospadias. Wolffian structures are normal but spermatogenesis is usually impaired.16

This condition is rare in the UK, but recognised in the Dominican Republic, where individuals are often reared as female and convert to male in puberty, when body habitus and psychosexual orientation becomes male. Virilisation improves but is incomplete.

A biochemical diagnosis is made by showing a ratio of T:DHT >30 after puberty or following hCG stimulation before puberty, and the ratio of 5α:5β metabolites in a urine steroid profile will be increased after 6 months of age. The urinary 5α:5β metabolites can also be used if the gonads have been removed. The diagnosis is confirmed by screening for mutations in the 5α-reductase type II gene (SRD5A2).

A 46XY karyotype, low basal and hCG stimulated testosterone levels with increased testosterone precursors indicates a testosterone biosynthetic defect. Those forms of CAH that cause under-virilisation of male genitalia include 17α-hydroxylase/17,20-lyase and 3β-hydroxysteroid dehydrogenase deficiency (table 3).

The conversion of androstenedione to testosterone occurs predominantly in the gonad and a post-hCG stimulated ratio of androstenedione to testosterone of >20:1 suggests 17β-hydroxysteroid dehydrogenase deficiency. A urine steroid profile is generally not helpful in this diagnosis before puberty. Molecular analysis of the HSD III gene (HSD17B3) is sought as confirmation of the diagnosis.

End-organ unresponsiveness A 46XY karyotype with genital ambiguity, normal or increased basal and peak testosterone on hCG test, and a normal T:DHT ratio points to partial androgen insensitivity. There is a variable phenotype, and sex of rearing depends on the degree of phallic development, and sometimes cultural considerations. The child may benefit from a trial of topical DHT cream or intramuscular testosterone (for example using 12.5–25 mg, monthly for three months) on penile growth to help anticipate response in puberty.

The diagnosis is suggested by showing an abnormality in androgen binding in genital skin fibroblasts, or a mutation in the androgen receptor gene. This requires DNA and a genital skin biopsy, taken at the time of EUA or genital surgery. Despite clear evidence of a phenotype consistent with partial androgen PAIS and normal production and metabolism of androgens, only a minority of patients are found to have an androgen receptor gene mutation. The likelihood of finding a mutation is increased if there is a family history consistent with X linkage. The majority of XY infants with undervirilisation remain unexplained.

DNA analysis Many of the causes of genital ambiguity have a genetic basis, and in these cases genetic counselling will be required. For example, androgen insensitivity syndrome is X-linked recessive, and CAH is autosomal recessive. In addition, identification and characterisation of a number of mutations of the genes involved in sexual differentiation has resulted in DNA tests which can be used in prenatal diagnosis. Identification of carriers will facilitate genetic counselling.

Congenital adrenal hyperplasia Several laboratories within the UK will undertake DNA analysis for this condition. Once the diagnosis has been made, a DNA sample from the proband should be taken. If a gene mutation is identified, the carrier status of the parents may be determined and the family should be counselled about the possibility of antenatal screening of subsequent pregnancies, and of steroid treatment of the mother in an attempt to reduce virilisation of a subsequent affected female fetus. In the UK, antenatal diagnosis and treatment is offered as part of a national British Society for Paediatric Endocrinology and Diabetes supported study monitoring efficacy, short and long term side effects, and outcome measures.

Androgen insensitivity DNA analysis is now being undertaken in Cambridge as part of a molecular genetics service in collaboration with Professor Ieuan Hughes. Samples are only analysed following collection of clinical, biochemical, and histological data that are consistent with an androgen insensitive pathophysiology.

Suspected 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency DNA samples in patients with suspected 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency can also be processed through the Cambridge laboratory.

Unusual cases of sexual ambiguity Mutations of developmental genes such as DAX1, SOX9, and WT1 may account for rarer cases of sexual ambiguity. Samples should be taken and DNA extracted and either stored or forwarded to the relevant laboratories, depending on clinical suspicion.
ASSIGNMENT OF SEX OF REARING

A decision about the sex of rearing should be made as soon as is practicable, usually based on the internal and external genital phenotype and the results of the various investigations. Cultural aspects may also be important in cases of severe ambiguity. Assignment of sex of rearing can be extremely difficult, particularly as there is a paucity of data on long term outcome in this area.

In the case of a virilised female (usually CAH), there is usually the potential for fertility and these babies are usually raised as girls. This is much easier if the diagnosis of CAH is made early.

Decisions about nature and timing of any surgery are made with the family acknowledging the considerable psychological impact of having a child with genital ambiguity. There is considerable debate as to the optimal timing of any genital surgery. In the presence of marked clitoromegaly, clitoral reduction is usually undertaken in infancy. Lesser degrees of clitoral enlargement may be left until puberty when the child can be involved with the decision making. The timing of any vaginoplasty is dependent on the anatomy of the internal and external genitalia and influenced by the potential for fertility and these babies (usually CAH), there is usually the genetic relation of the family.

ACKNOWLEDGEMENTS

We thank Professor Ivan Hughes and Dr John Achermann for their helpful comments. Email address for Professor Hughes for mutation analysis and discussion on the androgen receptor, 5α-reductase deficiency, and 17β-hydroxysteroid dehydrogenase: iah1000@cam.ac.uk. Email address for Dr Achermann for mutation analysis and discussion on early androgen insensitivity syndrome yet to be defined in molecular terms or milder variants of testicular dysgenesis. Prompt counselling and investigations (with the backup of recognised biochemical and genetic laboratories) is essential. The decision of sex of rearing and the timing of surgery need careful consideration within a multidisciplinary environment with full informed consent of the family.

REFERENCES


www.archdischild.com
Consensus statement on management of intersex disorders
I A Hughes, C Houk, S F Ahmed, P A Lee, LWPE1/ESPE2 Consensus Group

Management of intersex disorders

The birth of an intersex child prompts a long term management strategy that involves a myriad of professionals working with the family. It is estimated that genital anomalies occur in 1 in 4500 births. There has been progress in diagnosis, surgical techniques, understanding psychosocial issues, and recognising and accepting the place of patient advocacy. The Lawson Wilkins Pediatric Endocrine Society (LWPS) and the European Society for Paediatric Endocrinology (ESPE) considered it timely to review the management of intersex disorders from a broad perspective, to review data on longer term outcome, and to formulate proposals for future studies. The methodology comprised establishing several working groups whose membership was drawn from 50 international experts in the field. The groups prepared prior written responses to a defined set of questions resulting from an evidence based review of published reports. At a subsequent gathering of participants, a framework for a consensus document was agreed. This paper constitutes its final form.

NOMENCLATURE AND DEFINITIONS
Advances in identification of molecular genetic causes of abnormal sex with heightened awareness of ethical issues and patient advocacy concerns necessitate a re-examination of nomenclature. Terms such as intersex, pseudohermaphroditism, hermaphroditism, sex reversal, and gender based diagnostic labels are particularly controversial. These terms are perceived as potentially pejorative by patients, and can be confusing to practitioners and parents alike. The term “disorders of sex development” (DSD) is proposed, as defined by congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.

The proposed changes in terminology are summarised in table 1. A modern lexicon is needed to integrate progress in molecular genetic aspects of sex development. As outcome data in individuals with DSD are limited, it is essential to employ precision when applying definitions and diagnostic labels. It is also appropriate to use terminology that is sensitive to the concerns of patients. The ideal nomenclature should be sufficiently flexible to incorporate new information yet robust enough to maintain a consistent framework. Terms should be descriptive and reflect genetic aetiology when available, and accommodate the spectrum of phenotypical variation. Clinicians and scientists must value its use and it must be understandable to patients and their families. An example of how the proposed nomenclature could be applied in a classification of DSD is shown in table 2.

Psychosexual development is traditionally conceptualised as three components. Gender identity refers to a person’s self representation as male or female (with the caveat that some individuals may not identify exclusively with either). Gender role (sex-typical behaviours) describes the psychological characteristics that are sexually dimorphic within the general population, such as toy preferences and physical aggression. Sexual orientation refers to the direction(s) of erotic interest (heterosexual, bisexual, homosexual) and includes behaviour, fantasies, and attractions. Psychosexual development is influenced by multiple factors such as exposure to androgens, sex chromosome genes, and brain structure, as well as social circumstance and family dynamics. Gender dissatisfaction denotes unhappiness with assigned sex. Causes of gender dissatisfaction are poorly understood, even among individuals without DSD. Gender dissatisfaction 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. Prenatal androgen exposure is clearly associated with other aspects of psychosexual development.

There are dose related effects on childhood play behaviour in girls with congenital adrenal hyperplasia (CAH), whereby those with the more severe mutations and marked genital virilisation play more with boys’ toys. Prenatal androgen exposure is also associated with other psychological characteristics such as maternal interest and sexual orientation. It is important to emphasise the separability of sex-typical behaviour, sexual orientation, and gender identity. Thus homosexual orientation (relative to sex of rearing) or strong cross-sex interest in an individual with DSD is not an indication of incorrect gender assignment. Understanding variations in psychosexual development in individuals with DSD requires reference to studies in non-human species that show marked but complex effects of androgens on sex differentiation of the brain and on behaviour. Outcomes can be influenced by timing, dose, and type of androgen exposure, receptor availability, and modification by the social environment.

Data from rodent studies suggest that sex chromosome genes may also influence brain structure and behaviour directly. However, studies in individuals with complete androgen insensitivity syndrome (CAIS) do not indicate a behavioural role for Y chromosome genes, although data are limited. Sex differences in brain structures have been identified across species, some of which coincide with pubertal onset, perhaps suggesting hormonal responsibility. The limbic system and hypothalamus, both playing a role in reproduction, show sex differences in specific nuclei but it is not clear when these differences emerge. Interpretation of sex differences is complicated by the effect of cell death and synaptic pruning on normal maturation and by effects of experience on the brain. Structure of the brain is not currently useful for gender assignment.

INVESTIGATION AND MANAGEMENT OF DSD
General concepts of care
Optimal clinical management of individuals with DSD should comprise the following:

- gender assignment must be avoided before expert evaluation in newborns

Abbreviations: CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; ESPE, European Society for Paediatric Endocrinology; LWPS, Lawson Wilkins Pediatric Endocrine Society; MGD, mixed gonadal dysgenesis; PAIS, partial androgen insensitivity syndrome
evaluation and long term management must be carried out at a centre with an experienced multidisciplinary team;

- all individuals should receive a gender assignment;
- open communication with patients and families is essential and participation in decision making is encouraged;
- patient and family concerns should be respected and addressed in strict confidence.

The initial contact with the parents of a child with a DSD is important, as first impressions from these encounters often persist. A key point to emphasise is that the DSD child has the potential to become a well adjusted, functional member of society. While privacy needs to be respected, DSD is not shameful. It should be explained to the parents that the best course of action may not initially be clear, 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, and web based information may be helpful, provided the content and focus of the information is balanced and sound (http://www.sickkids.ca/childphysiology/cpwp/genital/genitalintro.html).

Ample time and opportunity should be made for continued discussion with review of information previously provided.

### The multidisciplinary team

Optimal care for children with DSD requires an experienced multidisciplinary team which is generally found in tertiary care centres. Ideally, the team includes paediatric subspecialists in endocrinology, surgery or urology or both, psychology/psychiatry, gynaecology, genetics, neonatology, and, if available, social work, nursing, and medical ethics. Core composition will vary according to DSD type, local resources, developmental context, and location. Ongoing communication with the family primary care physician is essential. The team has a responsibility to educate other health care staff in the appropriate initial management of affected newborn infants and their families. For new DSD patients, the team should develop a plan for clinical management with respect to diagnosis, gender assignment, and treatment options before making any recommendations.

Ideally, discussions with the family are conducted by one professional with appropriate communication skills. Transitional care should be organised with the multidisciplinary team operating in an environment comprising specialists with experience in both paediatric and adult practice. Support groups have an important role in the delivery of care to DSD patients and their families (see appendix 1).

### Clinical evaluation

A family and prenatal history, a general physical examination with attention to any associated dysmorphic features, and an assessment of the genital anatomy in comparison with published norms needs to be recorded (table 3). Criteria that suggest DSD include:

- overt genital ambiguity (for example, cloacal extrophy);

### Table 1 Proposed revised nomenclature

<table>
<thead>
<tr>
<th>Previous</th>
<th>Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intersex</td>
<td>Disorders of sex development (DSD)</td>
</tr>
<tr>
<td>Male pseudohermaphrodite</td>
<td>Disorders of sex development (DSD)</td>
</tr>
<tr>
<td>Undervirilisation of an XY male</td>
<td>46,XY DSD</td>
</tr>
<tr>
<td>Undermasculinisation of an XY male</td>
<td>46,XY DSD</td>
</tr>
<tr>
<td>Female pseudohermaphrodite</td>
<td>Disorders of sex development (DSD)</td>
</tr>
<tr>
<td>Overvirilisation of an XX female</td>
<td>46,XX DSD</td>
</tr>
<tr>
<td>Masculinisation of an XX female</td>
<td>46,XX DSD</td>
</tr>
<tr>
<td>True hermaphrodite</td>
<td>Ovotesticular DSD</td>
</tr>
<tr>
<td>XX male or XX sex reversal</td>
<td>46,XX testicular DSD</td>
</tr>
<tr>
<td>XY sex reversal</td>
<td>46,XY complete gonadal dysgenesis</td>
</tr>
</tbody>
</table>

### Table 2 An example of a DSD classification

<table>
<thead>
<tr>
<th>Sex chromosome DSD</th>
<th>46,XY DSD</th>
<th>46,XX DSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) 45,X (Turner syndrome and variants)</td>
<td>(A) Disorders of gonadal (testicular) development</td>
<td>(A) Disorders of gonadal (ovarian) development</td>
</tr>
<tr>
<td>1. Complete gonadal dysgenesis (Swyer syndrome)</td>
<td>1. Ovotesticular DSD</td>
<td></td>
</tr>
<tr>
<td>2. Partial gonadal dysgenesis</td>
<td>2. Testicular DSD (eg, 5RY+, dup SOX9)</td>
<td></td>
</tr>
<tr>
<td>4. Ovotesticular DSD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(B) 47,XXY (Klinefelter syndrome and variants)</td>
<td>(B) Disorders in androgen synthesis or action</td>
<td>(B) Androgen excess</td>
</tr>
<tr>
<td>1. Androgen biosynthesis defect (eg, 17-hydroxysteroid dehydrogenase deficiency, 5a reductase deficiency, 5AR mutations)</td>
<td>1. Fetal (eg, 21-hydroxylase deficiency, 11-hydroxylase deficiency)</td>
<td></td>
</tr>
<tr>
<td>2. Defect in androgen action (eg, CAIS, PAIS)</td>
<td>2. Fetalplacental (aromatase deficiency, POR)</td>
<td></td>
</tr>
<tr>
<td>3. LH receptor defects (eg, Leydig cell hypoplasia, aplasia)</td>
<td>3. Maternal (luteoma, exogenous, etc)</td>
<td></td>
</tr>
<tr>
<td>4. Disorders of AMH and AMH receptor (persistent müllerian duct syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C) Other</td>
<td>(C) Other</td>
<td></td>
</tr>
<tr>
<td>(eg, severe hypospadias, cloacal extrophy)</td>
<td>(eg, cloacal extrophy, vaginal atresia, MURCS, other syndromes)</td>
<td></td>
</tr>
</tbody>
</table>

While consideration of karyotype is useful for classification, unnecessary reference to karyotype should be avoided; ideally, a system based on descriptive terms (for example, androgen insensitivity syndrome) should be used wherever possible.

AMH, anti-müllerian hormone; CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; MURCS, müllerian, renal, cervicothoracic somite abnormalities; PAIS, partial androgen insensitivity syndrome; POR, cytochrome P450 oxidoreductase.


- apparent female genitalia with an enlarged clitoris, posterior labial fusion, or an inguinal/labial mass;
- apparent male genitalia with bilateral undescended testes, microopenis, isolated perineal hypospadias, or mild hypospadias with undescended testes;
- a family history of DSD such as CAIS;
- a discordance between genital appearance and a prenatal karyotype.

Most causes of DSD are recognised in the neonatal period; later presentations in older children and young adults include: previously unrecognised genital ambiguity; inguinal hernia in a girl; delayed or incomplete puberty; virilisation in a girl; primary amenorrhoea; breast development in a boy; and gross and occasionally cyclical haematuria in a boy.

### Diagnostic evaluation

Considerable progress has been made over understanding the genetic basis of human sexual development, yet a specific molecular diagnosis is identified in only about 20% of cases of DSD. The majority of virilised 46,XX infants will have CAH. In contrast, only 50% of 46,XY children with DSD will receive a definitive diagnosis. Diagnostic algorithms do exist, but with the spectrum of findings and diagnoses, no single evaluation protocol can be recommended in all circumstances. Some tests, such as imaging by ultrasound, are operator dependent. Hormone measurements need to be interpreted in relation to the specific assay characteristics and to normal values for gestational and chronological age. In some cases serial measurements may be needed.

First line testing in newborns includes: karyotyping with X and Y specific probe detection (even when prenatal karyotype is available), imaging (abdomino-pelvic ultrasound), measurement of 17-hydroxyprogesterone, testosterone, gonadotropins, anti-mullerian hormone, serum electrolytes, and urinalysis. The results of these investigations are generally available within 48 hours and will be sufficient for making a working diagnosis. Decision making algorithms are available to guide further investigation. These include hCG and ACTH stimulation tests to assess testicular and adrenal steroid biosynthesis, urinary steroid analysis by GC mass spectroscopy, imaging studies, and biopsies of gonadal material. Some gene analyses are carried out in clinical service laboratories. However, current molecular diagnosis is limited by cost, accessibility, and quality control. Research laboratories provide genetic testing, including functional analysis, but may face restrictions on communicating results.

### Gender assignment in newborn infants

Initial gender uncertainty is unsettling and stressful for families. Expediting a thorough assessment and decision is required. Factors that influence gender assignment include the diagnosis, genital appearance, surgical options, need for life long replacement therapy, the potential for fertility, views of the family, and sometimes the circumstances relating to cultural practices. More than 90% of 46,XX CAH patients and all 46,XY CAIS assigned females in infancy identify as females. Evidence supports the current recommendation to raise markedly virilised 46,XX infants with CAH as female. Approximately 60% of 5α-reductase (5αRD2) deficient patients assigned female in infancy and virilising at puberty (and all assigned male) live as males. In 5αRD2 and possibly 17β-hydroxysteroid dehydrogenase (17βHSD3) deficiencies, where the diagnosis is made in infancy, the combination of a male gender identity in the majority and the potential for fertility (documented in 5αRD2, but unknown in 17βHSD3) should be discussed when providing evidence for gender assignment. Among patients with PAIS, androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with the sex of rearing in about 25% of individuals, whether raised male or female. Available data support male rearing in all patients with micropenis, taking into account equal satisfaction with assigned gender in those raised male or female, but no need for surgery, and the potential for fertility in patients reared male. The decision on sex of rearing in ovotesticular DSD should consider the potential for fertility based on gonadal differentiation and genital development, and assuming the genitalia are, or can be made, consistent with the chosen sex. In the case of mixed gonadal dysgenesis (MGD), factors to consider include prenatal androgen exposure, testicular function at and after puberty, phallic development, and gonadal location. Individuals with cloacal extrophy reared female show variability in gender identity outcome, but more than 65% appear to live as female.

### 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 undertake these procedures. Parents now appear to be less inclined to choose

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**Table 3** Anthrometric measurements of the external genitalia

<table>
<thead>
<tr>
<th>Sex</th>
<th>Population</th>
<th>Age</th>
<th>Stretched penile length (PL) (cm)</th>
<th>Penile width (cm)</th>
<th>Mean testicular volume (ml)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>USA</td>
<td>30 wks GA</td>
<td>2.5 (0.4)</td>
<td>1.1 (0.1)</td>
<td>0.52 (median)</td>
<td>26</td>
</tr>
<tr>
<td>M</td>
<td>USA</td>
<td>Full term</td>
<td>3.5 (0.4)</td>
<td>1.1 (0.1)</td>
<td>0.52 (median)</td>
<td>26</td>
</tr>
<tr>
<td>M</td>
<td>Japan</td>
<td>Term to 14 years</td>
<td>2.9 (0.4)</td>
<td>0.8 (0.8)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Australia</td>
<td>24-36 weeks GA</td>
<td>6.2 (0.7)</td>
<td>1.07 (0.09)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>China</td>
<td>Term</td>
<td>3.1 (0.3)</td>
<td>1.14 (0.07)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>India</td>
<td>Term</td>
<td>3.6 (0.4)</td>
<td>1.1 (0.08)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>USA</td>
<td>Adult</td>
<td>3.4 (0.3)</td>
<td>1.07 (0.09)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Europe</td>
<td>10 years</td>
<td>6.4 (0.4)</td>
<td>1.14 (0.07)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>USA</td>
<td>Adult</td>
<td>13.3 (1.6)</td>
<td>1.14 (0.07)</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD) unless specified.
*Distance from posterior fourchette to anterior anal margin.
GA, gestational age; PL, penile length.

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surgery for less severe clitoromegaly. Surgery should only be considered in cases of severe virilisation (Prader III, IV, and V) and should be carried out in conjunction, when appropriate, with repair of the common urogenital sinus. As orgasmic function and erectile sensation may be disturbed by clitoral surgery, the surgical procedure should be anatomically based to preserve erectile function and the innervation of the clitoris. Emphasis is on functional outcome rather than a strictly cosmetic appearance. It is generally felt that surgery that is carried out for cosmetic reasons in the first year of life relieves parental distress and improves attachment between the child and the parents. The systematic evidence for this belief is lacking.

There is inadequate evidence currently in relation to establishment of functional anatomy, to abandon the practice of early separation of the vagina and urethra. The rationale for early reconstruction is based on guidelines on the timing of genital surgery from the American Academy of Pediatrics (AAP), the beneficial effects of oestrogen on tissue in early infancy, and the avoidance of potential complications from the connection between the urinary tract and peritoneum through the Fallopian tubes. It is anticipated that surgical reconstruction in infancy will need to be refined at the time of puberty. Vaginal dilatation should not be undertaken before puberty. The surgeon must be familiar with several operative techniques in order to reconstruct the spectrum of urogenital sinus disorders. An absent or inadequate vagina (with rare exceptions) requires a vaginoplasty performed in adolescence when the patient is psychologically motivated and a full partner in the procedure. No one technique has been universally successful; self dilatation, skin substitution, and bowel vaginoplasty each have specific advantages and disadvantages.

In the case of a DSD associated with hypospadias, standard techniques for surgical repair such as chordae correction, urethral reconstruction, and the judicious use of testosterone supplementation apply. The magnitude and complexity of phalloplasty in adulthood should be taken into account during the initial counselling period if successful gender assignment is dependent on this procedure. At times this may affect the balance of gender assignment. Patients must not be given unrealistic expectations about penile reconstruction, including the use of tissue engineering. There is no evidence that prophylactic removal of asymptomatic discordant structures, such as a urticulus or Mullerian remnants, is required although symptoms in future may indicate surgical removal. For the male who has a successful neophalloplasty in adulthood, an erectile prosthesis may be inserted but has a high morbidity.

The tests in patients with CAIS and those with PAIS, raised female, should be removed to prevent malignancy in adulthood. The availability of oestrogen replacement therapy allows for the option of early removal at the time of diagnosis which also takes care of the associated hernia, psychological problems with the presence of testes, and the malignancy risk. Parental choice allows deferment until adolescence, recognising that the earliest reported malignancy in CAIS is at 14 years of age. The streak gonad in a patient 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. In patients with androgen biosynthetic defects raised female, gonadectomy should be undertaken 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 intra-tubular germ cell neoplasia. If positive, the option is sperm banking before treatment with local low dose radiotherapy which is curative.

Surgical management in DSD should also consider options that will facilitate the chances of fertility. In patients with a symptomatic utriculus, removal is best undertaken laparoscopically to increase the chance of preserving continuity of the vasa deferentia. Patients with bilateral oovestes are potentially fertile from functional ovarian tissue. Separation of ovarian and testicular tissue can be technically difficult and should be undertaken, if possible, in early life.

Sex steroid replacement

Hypogonadism is common in patients with dysgenetic gonads, defects in sex steroid biosynthesis, and resistance to androgens. The timing of initiation of puberty may vary but this is an occasion that provides an opportunity to discuss the condition and set a foundation for long term adherence to treatment. Hormonal induction of puberty should attempt to replicate 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; other options include oral testosterone undecanoate, and transdermal preparations are also available. Patients with PAIS may require supraphysiological doses of testosterone for optimal effect. Females with hypogonadism require oestrogen supplementation to induce pubertal changes and menses. A progestin is usually added after breakthrough bleeding develops or within one to two years of continuous oestrogen. There is no evidence that the addition of cyclic progestrone is beneficial in women without a uterus.

Psychosocial management

Psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management in order to promote positive adaptation. This expertise can facilitate team decisions about gender assignment/ reassignment, timing of surgery, and sex hormone replacement. Psychosocial screening tools that identify families at risk for maladaptive coping with a child’s medical condition are available. Once the child is sufficiently developed for a psychological assessment of gender identity, such an evaluation must be included in discussions about gender reassignment. Gender identity 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 behaviour 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 is required over a period of time. If the desire to change gender persists, the patient’s wish should be supported and may require the input of a specialist skilled in the management of gender change. The process of disclosure concerning facts about karyotype, gonadal status, and prospects for future fertility is a collaborative ongoing action which requires a flexible individual based approach. It should be planned with the parents from the time of diagnosis.

Studies in other chronic medical disorders and of adoptees indicate that disclosure is associated with enhanced psychosocial adaptation. Medical education and counselling for children is a recurrent gradual process of increasing
sophistication which is commensurate with changing cognitive and psychological development. Quality of life encompasses falling in love, dating, attraction, ability to develop intimate relationships, sexual functioning, and the opportunity to marry and to raise children, regardless of biological indicators of sex. The most frequent problems encountered in DSD patients are sexual aversion and lack of arousability, which are often misinterpreted as low libido. Health care staff should offer adolescent patients opportunities to talk confidentially without their parents and encourage the participation in condition specific support groups which enhance the ability of the patient to discuss their concerns comfortably. Some patients avoid intimate relationships and it is important to address fears of rejection and advise on the process of building a relationship with a partner. The focus should be on interpersonal relationships and not solely on sexual function and activity. Referral for sex therapy may be needed. Repeated examination of the genitalia, including medical photography, may be experienced as deeply shaming. Medical photography has its place for record keeping and education, but should be undertaken whenever possible if the patient is under anaesthesia for a procedure and with appropriate consent. Medical interventions and negative sexual experiences may have fostered symptoms of post-traumatic stress disorder and referral to a qualified mental health professional may be indicated.

OUTCOME IN DSD

As a general statement, information across a range of assessments is insufficient in DSD. The following is based on those disorders where some evidence base is available. They include CAH, CAIS and PAIS, disorders of androgen biosynthesis, gonadal dysgenesis syndromes (complete and partial), and microphallic. Long term outcome in DSD should include the following: external and internal genital phenotype, physical health including fertility, sexual function, social and psychosexual adjustment, mental health, quality of life, and social participation. There are additional health problems in individuals with DSD. These include the consequences of associated problems such as other malformations, developmental delay and intellectual impairment, delayed growth and development, and unwanted effects of hormones on libido and body image.

Surgical outcome

Some studies suggest satisfactory outcomes from early surgery. Nevertheless, outcomes from clitoroplasty identify problems related to decreased sexual sensitivity, loss of clitoral tissue, and cosmetic issues. Techniques for vaginoplasty carry the potential for scarring at the introitus, necessitating repeated modification before sexual function can be reliable. Surgery to construct a neo-vagina carries a risk of neoplasia. The risks from vaginoplasty are different for high and low confluence of the urethra and vagina. Analysis of long term outcomes is complicated by a mixture of surgical techniques and diagnostic categories. Few women with CAIS need surgery to lengthen the vagina.

The outcome in undermasculinised males with a phallus is dependent on the degree of hypospadias and the amount of erectile tissue. Feminising as opposed to masculinising genitalplasty requires less surgery to achieve an acceptable outcome and results in fewer urological difficulties. Long term data on sexual function and quality of life among those assigned female as well as male show great variability. There are no controlled clinical trials of the efficacy of early (less than 12 months of age) versus later surgery (in adolescence and adulthood), or of the efficacy of different techniques.

Risk of gonadal tumours

Interpretation of published reports is hampered by unclear terminology and by effects of normal cell maturation delay. The highest tumour risk is found in TSPY (testis-specific protein Y encoded) positive gonadal dysgenesis and PAIS with intra-abdominal gonads, while the lowest risk (<5%) is found in ovotestis and CAIS. Table 4 provides a summary of the risk of tumour development according to diagnosis and recommendations for management.

Cultural and social factors

DSD may carry a stigma. Social and cultural factors, as well as hormonal effects, appear to influence gender role in 5α-reductase deficiency. Gender role change occurs at different rates in different societies, suggesting that social factors may also be important modifiers of gender role change. In some societies, female infertility precludes marriage, which also affects employment prospects and creates economic dependence. Religious and philosophical views may influence how parents respond to the birth of an infant with a medical condition. Fatalism and guilt feelings in relation to congenital malformations or genetic conditions have an influence, while poverty and

Table 4 Risk of germ cell malignancy according to diagnosis

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Disorder</th>
<th>Malignancy risk (%)</th>
<th>Recommended action</th>
<th>Studies (n)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>GD (+Y); PAIS non-scrotal</td>
<td>15-35</td>
<td>Gonadectomy†</td>
<td>12</td>
<td>350</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Turner (+Y); 17hl-HSD; GD (+Y); PAIS scrotal gonad</td>
<td>28</td>
<td>Monitor</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Low</td>
<td>CAIS; Ovotestis DSD; Turner (−Y)</td>
<td>2</td>
<td>Biopsy and irradiation?</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>No (?l)</td>
<td>5α-reductase; Leydig cell hypoplasia</td>
<td>0</td>
<td>Unresolved</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).
†G8Y region positive, including the TSPF gene.
‡At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry.
CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; HSD, hydroxysteroid dehydrogenase deficiency; PAIS, partial androgen insensitivity syndrome.
### Table 5: Genes known to be involved in disorders of sex development: 46,XY

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>OMIM</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Gonad</th>
<th>Mullerian structures</th>
<th>External genitalia</th>
<th>Associated features/variant phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>46,XY DSD</strong> Disorders of gonadal (testicular) development: single gene disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT1</td>
<td>TF</td>
<td>607102</td>
<td>11p13</td>
<td>AD</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Female or ambiguous</td>
</tr>
<tr>
<td>SF1</td>
<td>Nuclear receptor TF</td>
<td>184757</td>
<td>9q33</td>
<td>AD/AR</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Female or ambiguous</td>
</tr>
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<td>SRY</td>
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<td>480000</td>
<td>Yp11.3</td>
<td>–</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Female or ambiguous</td>
</tr>
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<td>TF</td>
<td>608160</td>
<td>17q24-25</td>
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<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Female or ambiguous</td>
</tr>
<tr>
<td>DHX5</td>
<td>Signalling molecule</td>
<td>605423</td>
<td>12q13.1</td>
<td>AR</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>+</td>
<td>Female</td>
</tr>
<tr>
<td>ATRX</td>
<td>Helicase (chromatin remodelling)</td>
<td>300302</td>
<td>Xq13.3</td>
<td>X</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Female, ambiguous or male</td>
</tr>
<tr>
<td>ARX</td>
<td>TF</td>
<td>300382</td>
<td>Xp22.13</td>
<td>X</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Ambiguous</td>
</tr>
<tr>
<td><strong>Disorders of gonadal (testicular) development: chromosomal changes involving key candidate genes</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>DMR1</td>
<td>TF</td>
<td>602424</td>
<td>9p24.3</td>
<td>Monosomic deletion dupXp21</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Female or ambiguous</td>
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<tr>
<td>DAX1</td>
<td>Nuclear receptor TF</td>
<td>300018</td>
<td>Xp21.3</td>
<td>X</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>–</td>
<td>Female or ambiguous</td>
</tr>
<tr>
<td>WNT4</td>
<td>Signalling molecule</td>
<td>603490</td>
<td>1p35</td>
<td>dup1p35</td>
<td>Testis</td>
<td>Dygenetic tests</td>
<td>+</td>
<td>Female or ambiguous</td>
</tr>
<tr>
<td><strong>Disorders of hormone synthesis or action</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LHCGR</td>
<td>G protein receptor</td>
<td>152790</td>
<td>2p21</td>
<td>AR</td>
<td>Testis</td>
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<td>–</td>
<td>Female, ambiguous or micropenis</td>
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<tr>
<td>DHCR7</td>
<td>Enzyme</td>
<td>602858</td>
<td>11q12-13</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
<td>–</td>
<td>Variable</td>
</tr>
<tr>
<td>STAR</td>
<td>Mitochondrial membrane protein</td>
<td>600617</td>
<td>8p11.2</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
<td>–</td>
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</tr>
<tr>
<td>CYP11A1</td>
<td>Enzyme</td>
<td>118485</td>
<td>15q23-24</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
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<td>Female, ambiguous</td>
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<tr>
<td>HSD3B2</td>
<td>Enzyme</td>
<td>201810</td>
<td>1p13.1</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
<td>–</td>
<td>Ambiguous</td>
</tr>
<tr>
<td>CYP17</td>
<td>Enzyme</td>
<td>202110</td>
<td>10q24.3</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
<td>–</td>
<td>Female, ambiguous or micropenis</td>
</tr>
<tr>
<td>POR</td>
<td>(P450 oxidoreductase)</td>
<td>124015</td>
<td>7q11.2</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
<td>–</td>
<td>Male or ambiguous</td>
</tr>
<tr>
<td>HSD17B3</td>
<td>Enzyme</td>
<td>605573</td>
<td>9q22</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
<td>–</td>
<td>Female or ambiguous</td>
</tr>
<tr>
<td>SRD5A2</td>
<td>Enzyme</td>
<td>607306</td>
<td>2p23</td>
<td>AR</td>
<td>Testis</td>
<td>Testis</td>
<td>–</td>
<td>Ambiguous or micropenis</td>
</tr>
<tr>
<td>AMH</td>
<td>Signalling molecule</td>
<td>600957</td>
<td>19p13.3-13.2AR</td>
<td>Testis</td>
<td>Normal male</td>
<td>Normal male</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>AMH-Receptor</td>
<td>Serine-threonine</td>
<td>600956</td>
<td>12q13</td>
<td>AR</td>
<td>Testis</td>
<td>Normal male</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Nuclear receptor TF</td>
<td>313700</td>
<td>Xq11-12</td>
<td>X</td>
<td>Testis</td>
<td>Normal male</td>
<td>–</td>
<td>Female, ambiguous, micropenis or normal male</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; TF, transcription factor; X, X-linked recessive; Y, Y-linked recessive. Copyright 2002, The Endocrine Society.
illiteracy negatively affect access to health care.87

FUTURE STUDIES

Establishing a precise diagnosis in DSD is just as important as in other chronic medical conditions with lifelong consequences. Considerable progress has been achieved with molecular studies, as illustrated in tables 5 and 6, which summarise the genes known to be involved in DSD. Use of tissue specific animal knock out models, comparative genomic hybridisation, and microarray screens of the mouse urogenital ridge will provide benefits in identifying new genes causing DSD.88 It is essential that the momentum for an international collaborative approach to this task is maintained.

Much remains to be clarified about the determinants of gender identity in DSD. Future studies require representative sampling to carefully conceptualise and measure gender identity, recognising that there are multiple determinants to consider and gender identity may change into adulthood. In terms of psychological management, studies are needed to evaluate the effectiveness of information management with regard to timing and content. The pattern of surgical practice in DSD is changing with respect to the timing of surgery and the techniques employed. It is essential to evaluate the effects of early versus later surgery in an holistic manner, recognising the difficulties posed by an ever evolving clinical practice.

The consensus has clearly identified a major shortfall in information about long term outcome. Future studies should use appropriate instruments that assess outcomes in a standard manner38 69 and take cognisance of guidelines relevant to all chronic conditions (http://www.who.int/classifications/icf/en/). These should preferably be prospective in nature and designed to avoid selection bias. Several countries already have registers of DSD cases but there could be added benefit from pooling such resources to enable prospective multicentre studies to be undertaken on a larger number of cases that are clearly defined. Allied to this should be an educational programme to ensure that professionals tasked with providing care for DSD families are suitably trained to discharge their responsibilities.

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Table 6: Genes known to be involved in disorders of sex development: 46,XX

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>OMIM</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Gonad</th>
<th>Mullerian structures</th>
<th>External genitalia</th>
<th>Associated features/variant phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRX9</td>
<td>TF</td>
<td>480000</td>
<td>Yp11.3</td>
<td>Translocation</td>
<td>Tests or ovaries</td>
<td>ND</td>
<td>Male or ambiguous</td>
<td>Male or ambiguous</td>
</tr>
<tr>
<td>SOX9</td>
<td>TF</td>
<td>608160</td>
<td>17q24</td>
<td>dup17q24</td>
<td>ND</td>
<td>Male or ambiguous</td>
<td>Male or ambiguous</td>
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</tr>
<tr>
<td>HSD3B2</td>
<td>Enzyme</td>
<td>201810</td>
<td>1p13</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Citoromgaly</td>
<td></td>
</tr>
<tr>
<td>CYP21A2</td>
<td>Enzyme</td>
<td>201910</td>
<td>6q21-23</td>
<td>AR</td>
<td>Ovary</td>
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<td>Ambiguous</td>
<td></td>
</tr>
<tr>
<td>CYP11B1</td>
<td>Enzyme</td>
<td>202010</td>
<td>8q21-22</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td></td>
</tr>
<tr>
<td>POR (P450 oxidoreductase)</td>
<td>CYP enzyme electron donor</td>
<td>124015</td>
<td>7q11.2</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td></td>
</tr>
<tr>
<td>CYP19</td>
<td>Enzyme</td>
<td>107910</td>
<td>15q21</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid receptor</td>
<td>Nuclear receptor TF</td>
<td>138040</td>
<td>5q31</td>
<td>AR</td>
<td>Ovary</td>
<td>+</td>
<td>Ambiguous</td>
<td></td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropin; AD, autosomal dominant; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; ND, not determined; TF, transcription factor; X, X chromosomal; Y, Y chromosomal. Chromosomal rearrangements likely to include key genes are included. Modified from Achermann et al69, with permission from the Endocrine Society.


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APPENDIX 1

ROLE OF SUPPORT GROUPS

The value of peer and parent support for many chronic medical conditions is widely accepted, and DSDs, being life-long conditions which affect developmental tasks at many stages of life, are no exception.

Those affected by DSDs and parent members value the following:

- Peer support ends isolation and stigma, providing a context in which conditions are put into perspective, and where intimate issues of concern can be discussed safely with someone who has “been there.”
- Children who form relationships with peers and affected adults early in their lives benefit from a feeling of normalcy early on, with support in place well before adolescence. Adolescents often resist attempts to introduce them to peer support.
- Support groups can help families and consumers find the best quality care.

While clinical practice may focus on gender and genital appearance as key outcomes, stigma and experiences associated with having a DSD (both within and outside the medical environment) are more salient issues for many affected people.

Support groups complement the work of the health care team and, together, can help improve services. Initiatives by support groups have led to improvements in management of DSD and research directed towards clinically relevant issues. Dialogue between health care professionals and support groups, and collaboration as partners is to be encouraged.

APPENDIX 2

LEGAL ISSUES

Basic understanding of medical law will remain, even as research and clinical experience evolve in eutiology, diagnosis, and treatment. This appendix draws on practice in three countries on standards of medical negligence and patient informed consent. In the USA, the medical profession sets standards of care based on prevailing medical custom. However, a treatment may also be that used by a respected minority of practitioners.

USA

Informed consent in the USA was founded on the principle of battery, whereby it is an offence to violate another person’s bodily integrity without consent. Nowadays, most states are concerned with negligent non-disclosure to the patient. The standard of adequate disclosure may be physician based, requiring conduct of a reasonable practitioner, or it may be patient based, asking what a reasonable patient would find material. Physician based disclosure must include information about risks, alternatives, outcomes, and prognosis, with or without treatment.

US courts assume that parents know what is best for their child when parental authority applies to consent for the child (substituted judgement). Parental decisions are deferred to except in situations where potentially life saving treatment is withheld. Consent to treatment by a child is dependent on an understanding of its nature and consequences.

United Kingdom

Medical negligence in the United Kingdom defines treatment that falls below the standard expected of a reasonably competent practitioner. The standard of proof in court is whether negligence is demonstrated on the balance of probabilities. It is incumbent on the practitioner to demonstrate that treatment was consistent with a rationally defensible body of medical opinion. A shift in parental prerogative to consent to treatment was reflected in the Children Act 1989, in which parental rights were replaced by parental responsibilities. UK courts can intervene with orders made requiring or preventing a specific action related to the child. Age is not a barrier to

www.archdischild.com
informed consent, providing that a minor demonstrates an understanding of the issues sufficient to have the capacity to consent.

**Colombia**

Colombian law is noted for a reasoned set of guidelines advanced by the highest court in cases of DSD. A protocol was formulated for parental and physician intervention. The process of consent requires “qualified and persistent informed consent” over an extended period of time. Authorisation is given in stages to allow time for the parents to come to terms with their child’s condition. The court aimed to strike a balance between parental autonomy for those who did and those who did not want early surgery for their child, until there was clear evidence of harm in deferring surgery until the child was competent to decide. Parents cannot consent for children over 5 years of age, as by then children are deemed to have identified with a gender and so are considered to be autonomous.

**IMAGES IN PAEDIATRICS**

**Intraoral graphite tattoo**

Graphite pencils, in addition to their usual role as teaching tools, may cause traumatic injury and foreign body reaction, especially during early childhood.

A 5 year old healthy female patient was referred from the paediatric clinic because of her father’s concern about a blue lesion on the upper gum which has been increasing in size over four months. Intraoral examination showed an asymptomatic, firm, well defined, scalloped, blue-black macule measuring 15 mm × 5 mm involving the attached gingiva and extending apically to the mucogingival junction in the area labial to the maxillary left primary central and lateral incisors (fig 1). There was no associated inflammation and the lesion failed to respond to the blanching test. A periapical radiograph of the anterior maxillary region did not show any pathological changes. Differential diagnoses of foreign body pigmentation, melanocytic nevi, and malignant melanoma were considered. A full mucoperiosteal flap was raised, revealing abundance of granulation tissue, destruction of labial cortical bone to the central incisor, and residues of solid black granules (fig 2). Histopathology showed mild chronic inflammatory cell infiltrate with multinucleated giant cells. There was no evidence of cellular atypia and solid granules were consistent with pencil graphite.

The most common causes of exogenous localised oral pigmentation are amalgam tattoo, followed by graphite. Intraoral graphite implantation is common in the anterior palates of younger children; biopsy is mandatory to rule out malignancy.

**References**