Sex determination – it can get complicated!

This article seeks to describe the challenges faced in managing a baby born with ambiguous genitalia. The article gives a brief outline of the key determinants of sex, then focuses on the clinical and investigative management of an infant born with ambiguous genitalia. It emphasises the need for specialist and multidisciplinary input in managing this complex and sensitive condition.

Tafadzwa Makaya
MBChB, MMedSci, MRCPCH
Paediatric Specialist Registrar
Sheffield Children's Hospital

Neil Wright
MB, BChir, MD, FRCPCH,
Consultant Paediatric Endocrinologist
Sheffield Children's Hospital
n.p.wright@sheffield.ac.uk

Keywords

ambiguous genitalia; determinants of sex; congenital adrenal hyperplasia; virilisation

Key points

Makaya T., Wright N. Sex determination - it can get complicated! *Infant* 2010; 6(3): 93-99.

1. Ambiguous genitalia in a newborn is a medical and psychological emergency.
2. It is important that there is a multi-disciplinary input into the management of the patient and the family.
3. Examination and investigations of the infant are focused on establishing and assigning a gender for the baby and identifying an underlying diagnosis.
4. On-going management of the baby is determined by the diagnosis. Surgical intervention, where possible, can be delayed until puberty.

The first thing that parents usually want to know when a baby is born is whether it is a boy or a girl. They look expectantly at the midwife for that declaration, 'It's a boy!' or 'It's a girl!' Even when the parents-to-be have an idea of the expected sex of the child from information given to them from antenatal scans or amniocentesis, there is always an air of excitement about actually confirming the baby's sex when it is born. No wonder then that the birth of a baby with ambiguous genitalia is a situation that any obstetrician or midwife dreads. The normal practice of routinely announcing the baby's sex cannot immediately be made, and instead the team are faced with a medical and psychological emergency.

The clinical problem

Ambiguous genitalia falls under the umbrella term of Disorders of Sexual Development (DSD), previously referred to as intersex conditions. **TABLE 1** gives the previous and revised terminologies.

The Lawson Wilkins Paediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) suggested these changes to reflect advances in understanding of the pathophysiology of these conditions while being sensitive to the concerns of patients affected by them[1]. However, not all people are in agreement with the new terminology with some authors highlighting the fact that some individuals with DSD still find the new terms demeaning[2]. These are technical terms that help clinicians communicate and should be used with great care in communications with parents, where simpler explanations are more appropriate. The term 'intersex' is probably best avoided when speaking to families.

Incidence of DSD and ambiguous genitalia

Not all DSDs are obvious at birth (for example 45, X –Turner's syndrome, 46, XY – Complete Androgen Insensitivity). The phenotypic spectrum of DSD varies from milder forms such as undescended testes, micropenis, and hypospadias, to more severe forms where the child's genitalia are truly ambiguous. In approximately 1 in 4,500 children the child's sex is uncertain at birth[3].

The frequencies of the various categories of DSD vary. Congenital adrenal hyperplasia (CAH) is the most common

Previous	Revised
Intersex	DSD
Female pseudohermaphrodite	46, XX DSD
Male pseudohermaphrodite	46, XY DSD
True hermaphrodite	Ovotesticular DSD
XX male	46, XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

TABLE 1 Previous terminology and revised nomenclature of disorders of sexual development (DSD).

- Classical congenital adrenal hyperplasia (CAH) in females – 1 in 28, 000.
- Hypospadias (international prevalence) – 1 in 300 live male births[6]. These figures are comparable with reported UK rates[7]. From a clinical perspective the presence of unilateral or bilateral undescended testes (cryptochidism) with hypospadias greatly increases the possibility of a more complex underlying disorders of sexual development (DSD) – rather than it being a simple idiopathic hypospadias[8].
- Androgen insensitivity (AIS) – 1 in 40,000.
- Gonadal dysgenesis or true hermaphrodites in general are rare with an international incidence of 1 in 100,000. However a higher than usual incidence is well documented in Southern Africa[9].

TABLE 2 The incidence of some forms of disorders of sexual development (DSD).

Gene (locus)	Mutant phenotypes
Sex chromosomes:	
DAX1 (Xp21.3)	Gonadal dysgenesis, congenital adrenal hypoplasia
SRY (Yp11)	Gonadal dysgenesis
AR (Xq11-12)	46, XY DSD) complete or partial androgen insensitivity syndrome (Male pseudohermaphroditism)
Non-sex chromosomes:	
WT1 (11p13)	Fraiser syndrome, Denys-Drash syndrome, with Wilms' Tumour.
SF-1 (9q33)	Gonadal and adrenal dysgenesis
SOX9 (17q24)	Campomelic dysplasia, male gonadal dysgenesis or XY sex reversal
MIS, or AMH, type II receptor (12q12-13)	Persistent mullerian duct syndrome
MIS, or AMH (19p13)	Persistent mullerian duct syndrome
HSD17B3 (9q22)	46,XY DSD (Male pseudohermaphroditism)
SRD5A2 (5p15)	46, XY DSD (Male pseudohermaphroditism. Virilisation may occur at puberty)
CYP17 (10q24-25)	46, XY DSD (Male pseudohermaphroditism)
CYP21 (6q21.3)	46, XX DSD Congenital adrenal hyperplasia (female pseudohermaphroditism)
HSD3B2 (1p13.1)	Congenital adrenal hyperplasia
CYP11B1 (8q24)	Congenital adrenal hyperplasia
StAR (8p11.2)	Congenital lipoid adrenal hyperplasia

TABLE 3 Mutations in the genes involved in sex determination with associated anomalies.

cause of truly ambiguous genitalia in the newborn. An analysis of worldwide infant screening of 6.5 million newborns found an incidence of 1 in 15,000, with the highest frequency reported in babies of European Jewish, Hispanic, Slavic or Italian descent[4,5]. Mixed gonadal dysgenesis is the second most common cause of DSD. The incidence of specific forms of DSD is illustrated in **TABLE 2**.

Determinants of sex

Determination of sex is complex and involves various genes and hormones, as well as various environmental factors. It is essential to have a basic understanding of normal and abnormal sex differentiation to be able to direct investigation of a baby with ambiguous genitalia.

Genetic make-up is determined at the moment of conception and the chromosomal composition determines the differentiation of the gonads. In the presence of the Y chromosome (46, XY) the gonad develops into a testis, and in the absence of the Y chromosome and the presence of a second X chromosome (46, XX) the gonad develops into an ovary. However an increasing number of genes on other chromosomes are now being recognised as influential in gonadal differentiation.

Some of the genes that contribute to the early and late processes of sex determination and differentiation[10] are listed in **TABLE 3**. Mutations in these genes cause important clinical syndromes.

In summary, the best defined gene involved in gonadal differentiation is the sex determining region on the Y chromosome (SRY) on which is found the testis determining factor (TDF). Other influential genes are the SOX9 which regulates anti-mullerian hormone (AMH) transcription, steroidgenic factor 1 (SF-1), DAX1 (dosage sensitive sex reversal chromosone X), Wilms' tumour 1(WT1) and anti-mullerian hormone gene itself – also called the mullerian inhibiting substance (MIS) gene.

Gonadal determination sets the stage for *phenotypical* differentiation – that is the type of gonad present determines the differentiation or regression of the internal ducts: the mullerian (female) or wolffian (male) ducts. This second phase of genital differentiation is hormonally mediated. For example, in the male testosterone mediates the positive development of the wolffian ducts. Dihydrotestosterone (produced from testosterone by the action of 5-alpha reductase in target tissues) influences the differentiation of the penis and scrotal sacs. Both testosterone and dihydrotestosterone work through the androgen receptor (**FIGURE 1**).

Disruption of the complex hormonal interactions that determine the usual male or female phenotype following

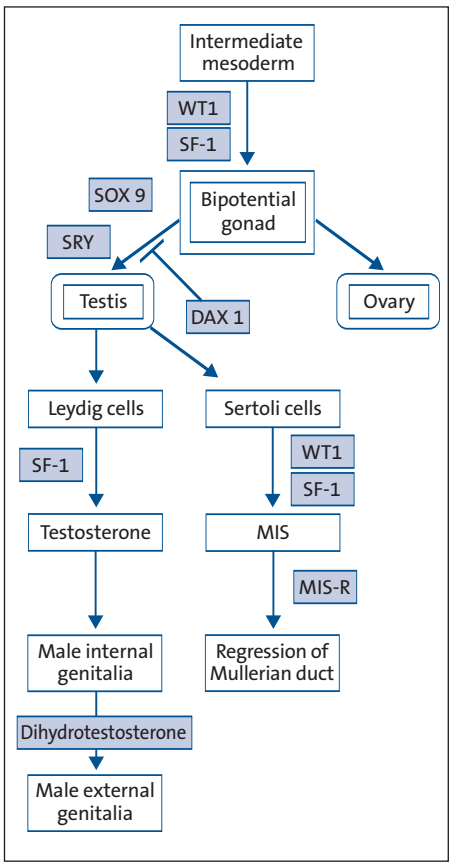

FIGURE 1 Factors involved in the determination of male sex.

differentiation of the gonad can therefore cause undervirilisation in males and overvirilisation in females. As the brief outline above suggests, it can get very complicated and is perhaps one of the most challenging areas for the paediatric endocrinologist. So consult with colleagues at the earliest opportunity.

The final aspect of the behavioural differentiation relates to *gender identity*. This is probably the most complex and least understood aspect relating to determination of sex. Gender identity is determined in part by the phenotypic appearance, and also by the brain's prenatal and postnatal development, and the environment[11]. The remaining components of human sexuality, including erotic responsiveness, sexual drive and choice of partners are incompletely understood[12]. The hormonal environment within the womb, patterns of rearing in childhood and complex poorly understood factors etc all influence an individual's gender identity. This will not however be obvious for many years and in the neonatal period the focus is on the phenotypic appearance and the assignment of gender.

Clinical approach to a baby with ambiguous genitalia

The delivery of a baby with ambiguous genitalia is devastating to parents and is also difficult for the medical team present. It requires prompt action by a multi-disciplinary team. The most important aspect is that no attempt should be made to guess the sex of the baby, and it must be clearly explained to parents that either a male or female gender will be determined once the pertinent results are available. It must be reinforced to parents that the results can take several weeks and hence registration of the baby's birth must be postponed until a definite gender has been determined. It is important for all staff dealing with the family to be sensitive to the difficult emotional processes the family are experiencing. Odd careless comments from staff can have devastating consequences towards how individuals perceive their newborn child. The family must be advised to avoid stereotyping colours or names. This can be particularly difficult if the family had an expectation of either a boy or a girl on the basis on an antenatal scan or amniocentesis as they have preconceived expectations.

The aim of assessment is to try and determine the gender of the baby, and establish an underlying diagnosis. It is vital that in a virilised female a diagnosis of CAH is excluded as the accompanying salt-losing crisis can be life threatening.

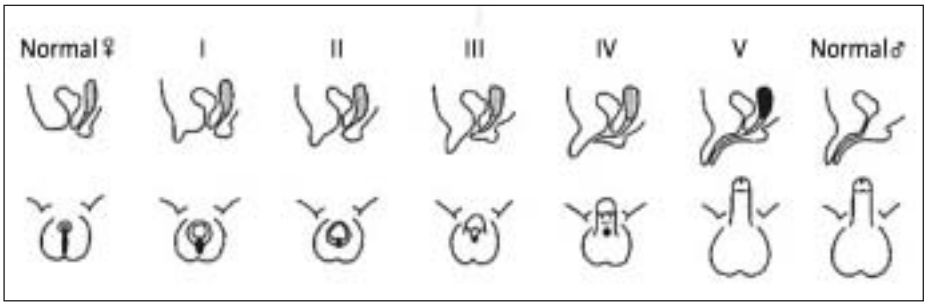

FIGURE 2 Prader staging of genitalia.

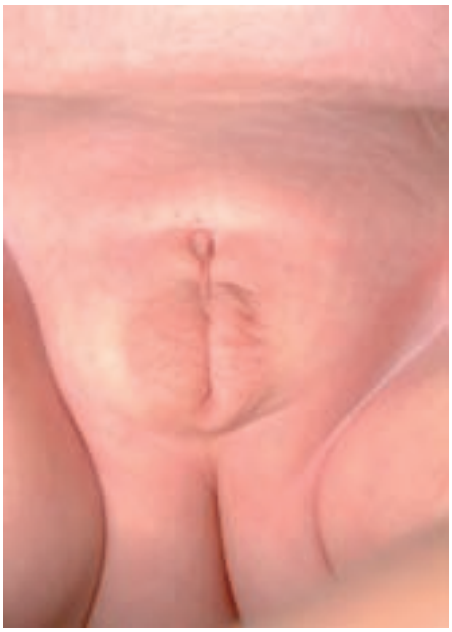

FIGURE 3 Micropenis in a newborn.

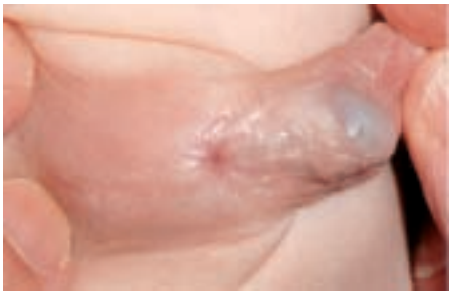

FIGURE 4 Ascertain location of urethral meatus.

History

This should be detailed and include the following:

- Details of the pregnancy: These should include a history of any maternal drug ingestion, in particular during the first trimester. Also remember to ask if the mother noticed any increase in body hair during the pregnancy. Maternal virilisation is important as it may suggest an androgen-producing maternal tumour or placental aromatisation of oestrogen to testosterone (rare).
- A history of any neonatal deaths as this may indicate an undiagnosed adrenal crisis or genetic disorder.
- A family history of ambiguous genitalia, unexpected changes at puberty or infertility. This needs to be specifically asked about as some families may not volunteer this information freely.
- A detailed family tree should be drawn and consanguinity should be noted if present.

Examination

- General examination: The baby should be assessed for any dysmorphic features, which could indicate an underlying genetic or chromosomal disorder. The skin should be inspected for excessive pigmentation, for example hyper-pigmented scrotum, suggesting excessive adrenocorticotropic hormone (ACTH). A blood pressure measurement should be taken as infants with the 11-betahydroxylase form of CAH tend to be hypertensive.
- External genital examination:
  - Prader staging is used to asses the degree of virilisation in females (**FIGURE 2**)
  - Size and differentiation of the phallus should be noted. A normal term neonatal penis is about 3cm stretched length. Variations may represent clitoromegaly or micropenis. Micropenis (**FIGURE 3**) is defined as a length of less than between 2.0-2.5cm, and it has been suggested that perhaps this definition should vary according to ethnicity[13]. Note the site of the urethral meatus and document any hypospadias (**FIGURE 4**).
  - Labioscrotal folds must be inspected for pigmentation levels and rugosity. The folds may be separated, or might be fused in the midline.
  - Note the presence or absence of a separate vaginal opening.

- Gonadal examination:
  - Document palpable gonads. In most patients only testicular material descends fully into the bottom of labioscrotal folds (although ovotestes have been reported to descend into the labioscrotal folds).
  - If there are palpable inguinal gonads certain diagnoses can be excluded (ie gonadal female, Turner syndrome and pure gonadal dysgenesis)
  - A complete lack of gonads on palpation even in an otherwise apparently normally virilised infant should always raise the possibility of a severely virilised 46,XX DSD patient with CAH for example.

Investigations

Taking bloods from the newborn baby can be difficult, therefore the tests need to be prioritised and ideally should be done after discussion with the laboratories and with specialists involved in the care of the infant. Key investigations suggested for the first day of life are listed in **TABLE 4**.

Further investigations can then only take place at around 48-72 hours of age (see **TABLE 5**). Checking the baby's hormones earlier than this makes results difficult to interpret because of maternal and placental hormones in the circulation. So despite everyone's desire to reach a rapid conclusion it is necessary to wait.

Further specialist investigations may be requested by the endocrinologists if required. Such investigations usually serve to confirm a diagnosis or provide further evidence in extremely complex cases. They do not usually necessitate the baby staying in hospital.

- Specialist investigations – as directed by sub-specialists:
  - Human chorionic gonadotropin (HCG) stimulation test: This is used to establish if there are functional Leydig cells present – cells able to produce testosterone in response to LH. It can also be used to assess for various blocks in the metabolic pathway of testosterone and for the presence/absence of tissue able to secrete testosterone.
  - Luteinsing hormone releasing hormone (LHRH) test: this may be more useful than one off FSH/LH levels as the gonadotrrophin response is difficult to assess in the prepubescent child.
  - Short synacthen test (SST): this is useful in cases of suspected CAH.
  - Examination under anaesthesia (EUA) or cystoscopy to determine the internal anatomy (usually not done for weeks/months if thought necessary).
  - Magnetic resonance imaging (MRI) or laparoscopy to locate gonads – though ultrasound is the most appropriate modality initially.

- Karyotype: This will determine the genetic make-up. The laboratories must be informed of the clinical urgency of processing the sample. Most sympathetic labs will perform a rapid FISH (Fluorescent *in situ* Hybridisation) test in advance of the karyotype if the clinical scenario is discussed with them directly, often turning it around within 24 hours. It is important to note that rarely there can be cases of mosaicism (eg XO/XY or XX,XY) and these may not always be apparent from the blood karyotype, but can be picked up on skin or gonadal biopsies.
- Chemistry samples including: urea and electrolytes, blood glucose levels, cortisol (and ACTH if enough blood)
- Urine dipstick for haematuria (Denys-Drash syndrome)
- Ultrasound scan of abdomen and pelvis: ensure a detailed clinical history on the request form to ensure that the radiographer is aware to look for and comment on gonads, mullerian structures, adrenal glands and renal structures. Both absence of expected internal structures and presence of unexpected structures are important. Staging of the internal structures also follows the Prader staging.

TABLE 4 Key initial investigations – Day 1 in child with ambiguous genitalia.

- Testosterone, oestradiol
- 17 hydroxyprogesterone, 11 deoxycortisol (exclude CAH)
- Adrenal androgens: androsterionedione, dehydroepiandrostenedione sulphates (DHEAS), dihydrotestosterone – looking for defects in the cascade of androgens that lead to the production of testosterone
- Gonadotropins: luteinising hormone (LH), follicle stimulating hormone (FSH). Neonates have a physiological 'mini-puberty', with gonadotropin levels peaking at 4-6 weeks post-delivery.
- Spot urinary steroid profile (USP)
- Consider: anti-mullerian hormone, inhibin B and renin – these can be helpful but are not always widely available. They can be checked later if needed.

TABLE 5 Further investigations (48-72hours age) – in order of priority.

Differential diagnosis

Initial test results will help determine if the infant is an over-virilised female (46, XX DSD) or an under-virilised male (46, XY DSD), which are the most likely scenarios.

Virilised female (46, XX DSD) – karyotype 46XX

- Congenital adrenal hyperplasia (CAH): Overall, this is the most common cause of truly ambiguous genitalia in newborns[14]. CAH presents with a spectrum of phenotypic virilisation but internal mullerian structures (uterus and fallopian tubes) are consistently present. The fundamental biochemical defect is an enzymatic block which results in deficient cortisol production. Feedback to the pituitary gland results in increased ACTH with consequent hypertrophy of the adrenal gland, and accumulation of the precursor hormones above the block. Clinical manifestation of CAH will usually depend on the specific enzyme block, however the degree of the block does not always correlate with the phenotype.

  21-hydroxylase deficiency accounts for 90% of patients with CAH[15]. It results in a mineralocorticoid deficiency and 75% of patients have salt-wasting nephropathy[16]. Diagnosis is by detection of elevated 17-hydroxprogesterone (17-OHP). Other forms of CAH due to enzyme blocks elsewhere in the pathway account for the remaining 10% and include:
  - 11-hydroxlase deficiency in which patients accumulate deoxycorticosterone (DOC) and 11-deoxycortisol. Patients exhibit salt retention and become hypertensive as DOC has strong mineralocorticoid activity.
  - 3-beta-hydroxysteroid dehydrogenase deficiency, which is quite rare and results in mild female virilisation and

undervirilisation in the male. It is the only form of CAH which can cause ambiguity in the genetic male. This is because the enzyme defect is present in both the adrenal and testicular tissue, resulting in inadequate levels of *in utero* testosterone. Patients present with salt losing.

- Maternal androgens:
  In these cases female fetuses may become virilised as a result of maternal use of progestagens or androgens during the first trimester.
- Maternal endocrine disorders such as ovarian tumours are a rare cause of virilisation in a female fetus as most of these conditions would usually prevent pregnancy.
- Placental aromatisation:
  Placental aromatase deficiency results in an inhibition of the conversion of androgens to oestrogens. This results in virilisation of a female fetus and maternal virilisation from the excessive fetal androgens, and the mother would typically report increased hairiness during the pregnancy.
- Ovotesticular DSD:
  In these cases (previously known as true hermaphrodite) both ovarian and testicular tissue are present. This condition accounts for less than 10% of DSD[17].The most common karyotype is 46, XX (70.6%) though mosaicism can occur[18]. A palpable gonad is present in 61% of patients, 60% of which are an ovotestis (Gonadal combinations may be any of testes, ovaries or ovotestes). Fertility has rarely been reported in ovotestes.

Undervirilised male (46, XY DSD) – karyotype 46 XY

- Ideopathic hypospadias:
  The cause of hypospadias remains unknown in the majority of patients. In up to 70% of cases, including even severe hypospadias, a cause is never identified. Reports indicate a multifactorial cause for the incidence of hypospadias with genetic, maternal, fetal and environmental triggers all implicated[6].
- Gonadal dysgenesis/malfunction:
  The gonads are abnormally developed. This condition can be classified as 46, XY DSD or as sex chromosome DSD if there is mosaicism (45, X/46, XY). The internal and external phenotype varies greatly, with some antenatally diagnosed mosaic newborns having normal male genitalia, others may exhibit a female phenotype.

  Investigations will show low baseline testosterone levels and a poor response to the HCG test. Gonadotrophins are usually elevated. The abnormal testes may produce sub-optimal levels of AMH and consequently hypoplastic or underdeveloped mullerian (internal female) structures may be present. There is a risk of gonadal malignant conversion in the dysplastic/streak gonads[19], and therefore surgery is usually indicated to remove these abnormal gonads.
- Biosynthetic defects:
  - Testosterone biosynthetic defect:
    Production of testosterone from cholesterol involves five enzymatic processes and defects have been identified at each step. Three of these enzymes (20-alpha hydoxylase, 3-beta-hydroxysteroid dehydrogenase and 17-alpha hydroxylase) are shared with the adrenal glands and consequently their deficiency will lead to ambiguous genitalia and symptoms of CAH. Rarer causes of deficiencies in testosterone production include Leydig cell hypoplasia/agenesis or inactivating mutations of the Leydig receptor.
  - 5-alpha-reductase deficiency:
    This results in a 46, XY fetus with normal testes but lacking the 5-alpha reductase enzyme required to convert testosterone to the more potent dihydrotestosterone (DHT). Infants are born with minimally virilised external genitalia including perineoscrotal hypospadias and small penis.
- End organ unresponsiveness:
  This includes partial androgen insensitivity, which will result in a spectrum of external phenotypes, from very feminine to more masculine. It is important to note that complete androgen insensitivity will result in an infant with a karyotype of 46, XY but completely female phenotype – NOT ambiguous genitalia.

Further management

On-going care of patients with ambiguous genitalia requires expert multidisciplinary input to discuss the various issues and support the family. The team should ideally include neonatologists, midwives, endocrinologists, clinical psychologists, geneticists and surgeons. The parents are an important part of this team, as are the GP, and the health visitor. It is vital that all members of the team are kept up-to-date with all the progress and results, and decisions.

- www.ukia.co.uk *(United Kingdom Intersex Association)*
- www.isna.org *(Intersex Society of North America)*
- www.also.org.au *(Intersex Society of Australia)*
- www.cah.org.uk *(Congenital Adrenal Hyperplasia UK Support Group)*
- www.aissg.org *(Androgen Insensitivity Syndrome Support Group UK)*

TABLE 6 Recommended websites for support and information.

Gender determination

The first step is to make a decision about the gender to be assigned to the child. This process is not always straightforward as there are various aspects to be considered including parental expectations, the phenotypical appearance and reproductive potential of the infant. Reproductive potential is usually determined by the quality and composition of the gonads present, and by the internal structures. There is a lot of pressure on the team to assign a gender quickly as having a baby with an unconfirmed gender is a huge stress on the family – but the key thing is to get it right.

In virilised females with CAH, which is the commonest reason for ambiguous genitalia with a 46XX karyotype, and on whom the remainder of this article will focus, there is reproductive potential and as such these children are usually assigned a female sex and reared as such. It would be unusual in the UK in even a severely virilised girl with CAH to consider assigning a male gender. The family will usually have a lot of questions, which they may find difficult to voice. Questions we are commonly asked include:

"Will my child be a tomboy?"

"Will my child be gay?"

"Will they be able to have sex?
Will they enjoy love-making?"

"Will they be able to have a child of their own?"

In more complex DSD cases it may not be possible for all these questions to be answered precisely. In girls with CAH though, we have a reasonably clear picture of the answers to many of these questions. Families may find it helpful to join support

groups or visit their websites. We tend to give the patients specific website addresses (**TABLE 6**) as some websites are of poor quality or promote an individual's opinion. Search engines tend to throw up pornographic websites which can be distressing for a family.

A key concern in girls with CAH is whether their developing brain, which is exposed to higher levels of testosterone *in utero*, leads them to develop male behaviour later. Girls with CAH do tend to have slightly more 'tomboy-like' behaviour in that they tend to favour playing with toys traditionally associated with boys such as guns and cars rather than dolls[20]. However this behaviour is not markedly different to healthy girls without CAH who may also be described as tomboys. Girls with CAH certainly identify themselves as female in the vast majority of cases. The majority form heterosexual relationships although there is perhaps a higher proportion that form same sex relationships compared to the general population[21].

Medical and surgical care

This will be tailored to meet the specific need of the underlying diagnosis. It is not possible within the scope of this article to discuss all aspects of the various forms of DSD. Children with CAH will need hormonal supplementation with glucocorticoids (hydrocortisone) and mineralocorticoids (fludrocortisone). Typically hydrocortisone is prescribed three times daily. In the neonatal period in particular, girls with evidence of salt loss, often need salt supplementation in addition to mineralocorticoids because of the relative immaturity of the kidney. It is usually possible though to discontinue salt supplements by 6-12 months of age.

Growth is closely monitored in both girls and boys with CAH as the relative excess of male hormones tends to cause an advance in the bone age with earlier fusion of the epiphyses. Meta-analysis suggests that overall children with CAH are likely to be 7-8 cm shorter than they otherwise would have been had they not had the condition[22].

The other key aspect of the management of a girl with CAH is the extent and timing of surgery. One of the difficulties in assessing how best to manage these girls from a surgical perspective is the lack of good long-term follow-up studies. Surgical techniques and approaches have changed over the years but the key outcomes of the adequacy of the vagina to permit sexual intercourse and the satisfaction women report from intercourse are difficult to assess in part because of the outcomes can only be ascertained in adult life and historically surgery has often been undertaken in childhood. Few studies have inquired as to sexual satisfaction. It is a contentious area and there are still a number of different views as to how girls should be managed particularly around the timing of surgery.

Surgical care in CAH

In more severely virilised girls there are usually two aspects to the problem. The first is the enlargement of the clitoris under the influence of higher levels of testosterone exposure *in utero*. The second is the fusion of the urethra and vagina to form a single, common urogenital passageway. Surgical intervention to separate the urethra and reconstruction of the vagina and introitus sufficient to permit intercourse is typically required.

Historically surgical practice has tended towards early clitoral reduction and tidying up of the external genitalia by way of feminising genitoplasty to present a more 'normal' looking appearance to the external genitalia. In many cases vaginal reconstruction was also undertaken in infancy. Longer term there have been concerns that clitoral surgery may impair sensation and reduce subsequent sexual satisfaction[23]. Many individuals who have had early vaginal reconstructive surgery subsequently require revision because of scarring and vaginal stenosis[24]. Many patients have expressed the feeling that early surgery denies them the opportunity to contribute to the decision-making process.

There remains much debate about the timing and the technical approach that should be adopted in individuals with virilising CAH[25]. Clitoral reduction involves removing part of the erectile tissue while preserving the glans and neurovascular bundle. There are arguments for delaying surgery until the child is older and can be part of the decision-making process[26], while others argue that corrective surgery should be performed before the child is school-going age[27], so they do not feel different from other children around them. There is a lack of controlled trials to assess the difference in early versus late surgery. The recent consensus guidelines suggest that feminising genitoplasty should not be carried out in all cases but should be reserved for those with more significant degrees of virilisation[28]. Individuals with minor degrees of clitoral hypertrophy may not require surgical reduction. They recommend that where feminising genitoplasty is carried out in infancy that separation of vagina and urethra should be undertaken at the same time – while accepting that in most cases further vaginal reconstruction will be required around puberty[28].

Data on long-term outcomes reflect historical surgical and clinical practices. The data are poor and the outcomes reported very variable. The cohort described by Al-Bassam (52 patients 1985-2001) reported a satisfactory clitoris in 78% and satisfactory vaginoplasty in 84% but none were sexually active[29]. In the cohort described by Creighton (21 patients – 1979-95) 24% were described as acceptable cosmetically, 65% were unable to use tampons and in 80% the introitus was inadequate for penetration[24]. There is now a keener appreciation of the importance of the patient view and of longer-term outcomes and so future generations should fare much better.

Another key question is that of fertility and pregnancy. Historically it was considered unlikely that women with CAH would be able to have children, but the Middlesex series showed that of 12 women who sought pregnancy, 11 were successful (five spontaneous, four with clomiphene and two post adrenalectomy) so there is reason to be cautiously optimistic about the potential for future pregnancy with families[30].

Summary

A lot of psychological support is required for the family of a child with ambiguous genitalia. There is usually a sense of grief experienced by the parents as they work through the emotions related to not having a 'perfect baby', and the expectations of the family and social units around them. They will need support during the processes of gender assignment, medical and surgical intervention described above. It is a complex area and it is essential that an experienced multidisciplinary team is involved early. Significant advances have been made in the medical and surgical management but a skilled and experienced team is required to optimise the outcome and support the family.

References

1. **Hughes I.A. et al.** Consensus statement on the management of intersex conditions. *J Ped Urol* 2006; **3**: 148-62.
2. **Italiano M., Hinkle C.E.** Ambiguous Medicine and Sexist Genetics: A critique of the DSD Nomenclature. Organisation Intersex International: Health and Sciences Resources. 2008, August http://www.intersexualite.org/sexist_genetics.html
3. **Hamerton J.L., Canning N., Ray M. et al.** A cytogenetic survey of 14, 069 newborn infants. Incidence of chromosome abnormalities. *Clin Genet* 1975; **4**: 223-43.
4. **Pang S., Clark A.** Newborn screening, prenatal diagnosis, and prenatal treatment of congenital adrenal hyperplasia due to 21-hyroxylase deficiency. *Trends Endocrinol Metab* 1990; **1**: 300-07.
5. **Speiser P.W., Dupont B., Rubeinstein P. et al.** High frequency of non-classical steroid 21-hydroxylase deficiency. *Am J Hum Genet* 1985; **37**: 650-67.
6. **Madhok N., Scharbach K., Shahid-Saless S.** Hypospadias. *Pediatric Rev* 2009; **30**(6): 235-37.
7. **Abdullah N.A., Pearce M.S., Parker L. et al.** Birth prevalence of cryptochidism and hypospadias in northern England, 1993-2000. *Arch Dis Child* 2007; **92**(7): 576-79.
8. **Kaefer M., Diamond D., Hendren W.H. et al.** The incidence of intersexuality in children with cryptochidism and hypospadias: stratification based on gonadal palpability and meatal position. *J Urol* 1999; **16**(3 Pt 2): 1003-06; discussion 1006-07.
9. **Wiersma R.** True hermaphroditism in Southern Africa: the clinical picture. *Pediatric Surg Int* 2004; **20**(5): 363-68.
10. **MacLaughlin D.T., Donahoe P.K.** Sex determination and differentiation. *N Engl J Med* 2004; **350**: 367-78.
11. **Reiner W.G., Gearhart J.P.** Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. *N Engl J Med* 2004; **350**: 333-41.
12. **Ferderman D.D.** Three facets of sexual differentiation. *N Engl J Med* 2004; 350: 323-24.
13. **Cheng P.S., Chanoine J.P.** Should the definition of micropenis vary according to ethnicity? *Horm Res* 2002; **55**: 278-81.
14. **Lorini R., Maghnie M., D'Annunzio G. et al.** Congenital Endocrinopathies; New insights into Endocrine Disorders and Diseases. Endocrine Development. Basel: Karger. 2007:(11):47-57.
15. **White P.C., Speiser P.W.** Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev* 2000; **21**(3): 245-91.
16. **Speiser P.W., White P.C.** Congenital adrenal hyperplasia. *N Engl J Med* 2003; **349**: 776-88.
17. **Hutcheson J., Snyder H.M.** Ambiguous genitalia and intersexuality. eMedicine Paediatrics: Surgery. Jul 16, 2009. http://emedicine.medscape.com/article/1015520 – overview. Last accessed 02/02/2010.
18. **Ogilvy-Stuart A.L., Brain C.E.** Early assessment of ambiguous genitalia. *Arch Dis Child* 2004; **89**: 401-07.
19. **Piggott H.W.S**. Malignant gonadal tumour formation in intersexual states. *Postgrad Med J* 1975; **51**: 252-55.
20. **Meyer-Bahlburg H.F.** Gender and sexuality in classic congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am* 2001; **30**(1): 155-71.
21. **Meyer- Bahlburg H.F., Dolezal C., Baker S.W., New M.I.** Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess. *Arch Sex Behav* 2008; **37**(1): 85-99.
22. **Eugster E.A., Dimeglio L.A., Wright J.C., Freidenberg G.R., Seshadri R., Pescovitz O.H.** Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. *J Pediatr* 2001; **138**(1): 26-32.
23. **Crouch N., Liao L., Woodhouse C. et al.** Sexual function and genital sensitivity following feminising genitoplasty for congenital adrenal hyperplasia. *J Urol* 2008; **179**(2): 634-38.
24. **Creighton S.M., Minto C.L., Steele S.J.** Objective cosmetic and anatomical outcomes at adolescence of feminising surgery for ambiguous genitalia done in childhood. *Lancet* 2001; **358**(9276): 124-25.
25. **Creighton S., Minto C.** Managing intersex. *BMJ* 2001; **323**: 1264-65.
26. **Karkazis K.** Fixing sex: Intersex, Medical Authority and Lived experience. 2008.
27. **Kirtane J.** Ethics in intersex disorders. *Issues Med Ethics* 2000; **8**(2): 47-48.
28. **Hughes I.A., Houk C., Ahmed S.F., Lee P.A.** Consensus statement on management of intersex disorders. *Arch Dis Child* 2006; **91**: 554-63.
29. **Al-Bassam A., Gado A.** Feminizing genital reconstruction: experience with 52 cases of ambiguous genitalia. *Eur J Pediatr Surg* 2004; **14**(3): 172-78.
30. **Ogilvie C.M., Crouch N.S., Rumsby G., Creighton S.M., Liao L.M., Conway G.S.** Congenital adrenal hyperplasia in adults: a review of medical, surgical and psychological issues. *Clin Endocrinol* 2006; **64**(1): 2-11.