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.

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.

TABLE 1

<table>
<thead>
<tr>
<th>Previous Terminology</th>
<th>Revised Terminology</th>
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<tbody>
<tr>
<td>Intersex</td>
<td>DSD</td>
</tr>
<tr>
<td>Female pseudohermaphrodite</td>
<td>46, XX DSD</td>
</tr>
<tr>
<td>Male pseudohermaphrodite</td>
<td>46, XY DSD</td>
</tr>
<tr>
<td>True hermaphrodite</td>
<td>Ovotesticular DSD</td>
</tr>
<tr>
<td>XX male</td>
<td>46, XX testicular DSD</td>
</tr>
<tr>
<td>XY sex reversal</td>
<td>46, XY complete gonadal dysgenesis</td>
</tr>
</tbody>
</table>

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. 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. 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.

The frequencies of the various categories of DSD vary. Congenital adrenal hyperplasia (CAH) is the most common
Classical congenital adrenal hyperplasia (CAH) in females – 1 in 28,000.

Hypospadias (international prevalence) – 1 in 300 live male births. These figures are comparable with reported UK rates. From a clinical perspective the presence of unilateral or bilateral undescended testes (cryptorchidism) with hypospadias greatly increases the possibility of a more complex underlying disorders of sexual development (DSD) – rather than it being a simple idiopathic hypospadias.

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.

Factors involved in the determination of male sex

Determinants of sex

Determinations 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.

Some of the genes that contribute to the early and late processes of sex determination and differentiation 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, steroidogenic factor 1 (SF-1), DAX1 (dosage sensitive sex reversal chromosome 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

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. 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

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Gene (locus) Mutant phenotypes

| Sex chromosomes: | | |
|------------------|------------------|
| DAX1 (Xp21.3)   | Gonadal dysgenesis, congenital adrenal hyperplasia |
| SRY (Yp11)      | Gonadal dysgenesis |
| AR (Xq11-12)    | 46, XY DSD (complete or partial androgen insensitivity syndrome) (Male pseudohermaphroditism) |

Non-sex chromosomes:

| WT1 (11p13)   | Fraser syndrome, Derys-Drash syndrome, with Wilms’ Tumour. |
| SF-1 (9q33)   | Gonadal and adrenal dysgenesis |
| SOX9 (19q24)  | Camptomelic 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 |
| HSD1B3 (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 (16q21.3) | 46, XX DSD (female pseudohermaphroditism) |
| HSD3B2 (1p13.1) | Congenital adrenal hyperplasia |
| CYP11B1 (8q24) | Congenital adrenal hyperplasia |
| STAR (8p11.2) | Congenital adrenal hyperplasia |

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

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.

FIGURE 1

Factors involved in the determination of male sex.

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

TABLE 3 Mutations in the genes involved in sex determination with associated anomalies.
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. The remaining components of human sexuality, including erotic responsiveness, sexual drive and choice of partners are incompletely understood. 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. A blood pressure measurement should be taken as infants with the 11-beta hydroxylase form of CAH tend to be hypertensive.

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 hyperpigmented scrotum, suggesting excessive adrenocorticotropic hormone (ACTH). 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.

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.

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- External genital examination:

  - Prader staging is used to assess 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. 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.
**Ambiguous Genitalia**

- **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.
  - Luteinising hormone releasing hormone (LHRH) test: this may be more useful than one off FSH/LH levels as the gonadotrophin 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.

**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. 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. It results in a mineralocorticoid deficiency and 75% of patients have salt-wasting nephropathy. Diagnosis is by detection of elevated 17-hydroxyprogesterone (17-OHP). Other forms of CAH due to enzyme blocks elsewhere in the pathway account for the remaining 10% and include:
    - 11-hydroxylase deficiency in which patients accumulate deoxycorticosterone (DOC) and 11-deoxycorticisol. 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...

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

<table>
<thead>
<tr>
<th>Testosterone, oestradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 hydroxyprogesterone, 11 deoxycortisol (exclude CAH)</td>
</tr>
<tr>
<td>Adrenal androgens: androsteronedione, dehydroepiandrosterone sulphates (DHEAS), dihydrotestosterone – looking for defects in the cascade of androgens that lead to the production of testosterone</td>
</tr>
<tr>
<td>Gonadotropins: luteinising hormone (LH), follicle stimulating hormone (FSH). Neonates have a physiological ‘mini-puberty’, with gonadotropin levels peaking at 4-6 weeks post-delivery.</td>
</tr>
<tr>
<td>Spot urinary steroid profile (USP)</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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

| Examination under anaesthesia (EUA) or cystoscopy to determine the internal anatomy. |
| Magnetic resonance imaging (MRI) or laparoscopy to locate gonads – though ultrasound is the most appropriate modality initially. |
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  - 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 maternal virilisation from the excessive fetal androgens, and the mother would typically report increased hairiness during the 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 usually present with salt losing.

• 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. The most common karyotype is 46, XX (70.6%) though mosaicism can occur. 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 hypospasias:
The cause of hypospasias remains unknown in the majority of patients. In up to 70% of cases, including even severe hypospasias, a cause is never identified. Reports indicate a multifactorial cause for the incidence of hypospasias with genetic, maternal, fetal and environmental triggers all implicated.

• 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 tests may produce sub-optimal levels of AMH and consequently hypoplastic or under-developed Mullerian (internal female) structures may be present. There is a risk of gonadal malignant transformation in the dysplastic/streak gonads, 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 hydroxylase, 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.

**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

- 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.
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 dolls21.
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
population22.

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
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 condition22.

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
satisfaction23. Many individuals who have
had early vaginal reconstructive surgery
subsequently require revision because of
scarring and vaginal stenosis24. 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 CAH25. 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 process26, while others
argue that corrective surgery should be
performed before the child is school-going
age27, 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 virilisation26. 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 puberty26.

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 active26. 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 penetration26. 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
cloimiphene and two post adrenalectomy)
so there is reason to be cautiously
optimistic about the potential for future
pregnancy with families26

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.