**Section 1: GROWTH AND DEVELOPMENT**

**Editors: Meg Keil and Kate Davies**

**Chapter 3: Disorders of Sex Development (DSD)**

**Author**

**Kate Davies RN (Child) Dip HE, BSc (Hons), MSc, NMP, PGCert, PGDip**

**Senior Lecturer in Children’s Nursing, London South Bank University, London, UK**

**Email:** kate.davies@lsbu.ac.uk

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**Abstract**

The diagnosis of a DSD – a disorder of sex development – whether made in infancy or as a young person – involves a full multidisciplinary team. Progress has been made in recent years with the advances of nomenclature, treatment and psychological approaches and the disorders have been categorised into more patient friendly terminology, leaving behind confusing and upsetting labels and stigma. These predominant DSD will be discussed in accordance with the new categories, detailing clinical presentation, management and nursing considerations in order to implement best practice. Emphasis here is placed on a fully co-operative multidisciplinary team, but also the nurses’ role, who can offer continued support and guidance to the child / young person and their families.

**Key Words**

Ambiguous genitalia

Chromosome

DSD

Gonads

Karyotype

**Key points**

1. Health care professionals involved in DSD care should follow the international consensus guidelines in order to offer optimum care.
2. A diagnostic pathway should be followed, whether the child is presenting in infancy or in adolescence
3. A full multidisciplinary team should be in place in order to fully support and guide the family in the treatment needed.
4. Paediatric endocrine nurses are in prime position to be the key advocate and liaison for the child / young person and their family.

**Key terms**

* Disorder of sex development: An umbrella term used to describe a group of conditions that involve the internal reproductive system and/or external genitalia (previously known as *Intersex*)
* Ambiguous genitalia: Where the genitals do not appear to be clearly either male or female.
* Diagnostic pathway: This is a kind of clinical tool, or map, to enable quality in the healthcare that is delivered, based on evidence based practice.
* Gonadal dysgenesis: Where the gonads (ovaries or testes) are made of mainly fibrous tissue, are undeveloped and do not function.
* Multidisciplinary team: A group of healthcare professionals from different professions, all providing their specific services for one patient.

**Abbreviations**

5 alpha reductase deficiency (5αRD)

11-deoxycortisol (11-DOC)

17 alpha-hydroxyprogesterone (17-OHP)

21- hydroxylase deficiency (21-OHD

Androgen Insensitivity Syndrome (AIS)

Androstenedione (A4)

Adrenocorticotrophic hormone (ACTH)

Anti-mullerian hormone (AMH)

Clinical Nurse Specialist (CNS)

Complete androgen insensitivity syndrome (CAIS)

Congenital Adrenal Hyperplasia (CAH)

Dehydroepiandrosterone (DHEA)

Dihydrotestosterone (DHT)

Disorder of Sex development (DSD)

Fluorescence in situ hybridization (FISH)

Follicle stimulating hormone (FSH)

General Practitioner (GP)

Gonadotrophic releasing hormone (GnRH)

Human chorionic gonadotrophin (HCG)

Luteinizing hormone (LH)

Mayer-Rokitansky-Küster-Hauser syndrome (MRKH)

Mullerian, renal, cervicothoracic somite abnormalities (MURCS)

Mullerian-inhibiting substance (MIS)

Multidisciplinary team (MDT)

Neonatal intensive care unit (NICU)

Partial androgen insensitivity syndrome (PAIS)

Paediatric endocrine nurse specialist (PENS)

Polycystic ovarian syndrome (PCOS)

Turner Syndrome (TS)

United Kingdom (UK)

**4.1. What is a DSD**

Disorders or Differences of Sex Development (DSD) is a phrase used to describe a multitude of congenital conditions in where the physical development of either the chromosomes, the gonads, (ie the ovaries or the testes), or anatomy is unusual or atypical. (1) It can also be described as where there is a difference between someone’s ‘genetic sex’ to how their internal or external reproductive systems appear (2). Many people use the term ‘disorder’, but that can lead some people to think of ‘ill’ children, so ‘differences’ is sometimes used instead. The incidence of actual ambiguous genitalia can occur in 1 in every 5000 live births (1), and is relatively rare. However, if all genital anomalies are to be considered, then a DSD can occur in approximately 1 in every 300 births (1). It is difficult to estimate exactly how many conditions come under the DSD umbrella: as the cause of a DSD is quite often a gene regulation breakdown (3) which is responsible for gonadal development, there is the potential for more genetic variants yet to be identified, plus there are also a number of rare multiple malformation syndromes associated with DSD. However, a recent international consensus statement (4) has identified a useful classification tool for DSD.

**4.2. Nomenclature**

Previously to this consensus statement, various terms were used to describe different DSD conditions. Due to further developments in genetics, ethical considerations, patient advocacy voices, as well as patients from affected families, plus also specialists working in the field (5) it was deemed necessary to replace these terms. Such terms that used to be used were ‘intersex’, hermaphroditism and pseudohermaphroditism (6) (See Table 4.1) (INSERT). ‘Intersex’ used to be used as a broad term to describe a clinical picture of a child with ambiguous genitalia, whereas hermaphroditism was used to describe an individual with both testicular and ovarian tissue (7) and pseudohermaphrodites were either male with testicular tissue or female, with ovarian tissue. Such terminology was confusing, and often stigmatised patients and their families (6). The new classification can be seen in Table 4.2. (INSERT)

***46, XX DSD***

This category describes individuals were they possess the usual number of chromosomes (46), and two X chromosomes (female), but the external and/or internal sex ducts have not developed in the expected female way (2). For example, the baby may be born with a womb and fallopian tubes, but their clitoris may look like a small penis. The most common form is congenital adrenal hyperplasia (CAH) and 21-hydroxylase deficiency (21-OHD) (***see Chapter on CAH)***. However, other conditions also fall under this category, but can depend on disorders of ovarian development or androgen excess.

***46, XY DSD***

This is where the individual is born with a 46, XY (typically male) chromosomal make up, but, like the female 46, XX DSD, their internal or external structures have not developed in what should be expected for a male. The reasons for a 46, XY DSD are more varied and complex in comparison to a 46, XX DSD, but are usually attributed to the foetus being unable to produce or respond to testicular hormones (2)

***Sex Chromosome DSD***

The sex chromosome DSD is where there is sex chromosome aneuploidy – where there is an abnormal number of X or Y chromosomes (8) – with either an extra or missing chromosome. Here the gonad is affected, and therefore ambiguous genitalia may be present, with also puberty and perhaps fertility also affected.

**4.3 Chromosomes and Embryology**

It is important to comprehend the principles of sexual differentiation when discussing the foundations of any DSD, and there are three sequential stages: (See Box 4.1)

**INSERT Box 4.1. The stages of embryological differentiation** (9)

Specific genes around gestational age week 3 lead to the differentiation of the gonads (10), but it is now widely known that the SRY gene, which resides on the p arm of the Y chromosome, sends signals to ‘sex neutral’ tissue, to develop into testes (2). If this gene is missing, or does not work properly, then healthy testes will not develop. Gonads and internal (Wolffian and Mullerian ducts) and external genitalia will have similiar appearance around this time (7).

However, around gestational ages week 6 to 7, these undifferentiated gonads begin to separate: if a Y chromosome is present, the gonad will develop into a testis, and gonadal cells will segregate into testicular cords and interstitial tissue (9). The testicular cords are made up of somatic sertoli cells and germ cells, and it is these sertoli cells that produce anti-mullerian hormone (AMH) or mullerian inhibiting substance (MIS). AMH is responsible for the regression of the mullerian ducts. Testosterone is also made by the testes. In the *absence* of these two hormones, female anatomy is formed – as the mullerian ducts have not regressed – EVEN if a Y chromosome is present.

As seen in Figure 4.1, (INSERT) (11) mullerian ducts in an XX female will develop into female reproductive structures (except ovaries), and they grow because there is no AMH to block their development. Therefore: no exposure to AMH will enable the internal structures to develop into the upper end of the vagina, the cervix, the womb, and the fallopian tubes (2). Conversely, the wolffian ducts will develop into the epididymides, the two vas deferens, and the seminal vesicles, for the male reproductive system.

There are further hormonal influences that will have an impact on the development of the external genitalia. From around 8 weeks gestation, the male embryo will develop a penis from the genital tubercle, urethral folds will develop into the corpus spongiosum that surrounds the urethra, and the genital folds will also fuse to form the scrotum (7). This happens under the influence of a hormone called dihydrotestosterone (DHT), which is converted from testosterone. DHT is made when an enzyme called 5 alpha reductase is available (2). If a baby does *not* make DHT, then a vulva will form, involving a clitoris, and the labia minora and majora. It is interesting to note, however, that there is no difference between the size of the clitoris and penis before the 14th week gestation: phalli growth usually peaks in the third trimester, usually from around 28 weeks gestation (9).

This is now apparent to see how ambiguous genitalia can occur: why some children who are XY may have female external genitalia, or why XX females may appear male (2). It is, therefore, this presentation of a baby with ambiguous genitalia which will initiate a cascade of investigations and support for the child and family.

**4.4. Diagnostic pathway**

New guidance (12) was formed by the United Kingdom (UK) Society of Endocrinology advising on the evaluation of infants and adolescents presenting with a suspected DSD. This guidance principally focuses on the diagnostic approach rather than lifelong management, and it is from this guidance that UK DSD centres follow.

***Infants***

Any baby where the appearance of their genitalia provokes questioning surrounding sex assignment needs to be investigated. Careful and sensitive management is needed, and a suggested diagnostic pathway (13) is seen in Figure 4.2. (INSERT)

*Identification*

This is the first step where a suspected DSD in an infant is identified, usually by a midwife, or a paediatrician / obstetrician shortly after birth. It is essential that the baby is referred to a centre which has experience in DSD, and the referring personnel must contact the appropriate team which as much detail as possible, including:

Clinical status:

The referring team must describe if the baby is clinically well, for example, if they are ventilated, in an incubator, on antibiotics or intravenous fluids, or having problems with serum sodium or blood glucose levels.

Clinical history:

A detailed description of the genitalia is needed, such as any hyperpigmentation, labial fusion, urethral meatus position, hypospadias or chordee (where the head of the penis can curve upwards or downwards), and if the gonads are palpable. The Prader staging of external genitalia (Figure 4.3) (INSERT) is used to classify the degree of virilisation in external genitalia. Hypospadias descriptions can be classified by using the Hypospadias descriptions diagram (Figure 4.4) (INSERT), and the External Masculinisation Score is used to describe states of labial fusion and if and where the gonads are palpable (Figure 4.5) (INSERT)

Family history

Details from the family are needed, such as antenatal scans and results of prenatal testing, and if there is any maternal history, such as exposure to any medications or other environmental factors (14), or whether any assisted techniques for conception were used (15). Sensitive questioning is also needed enquiring of ethnicity, any parental consanguinity, or any history of unexplained infant deaths in the family or any other noted cases of DSD.

Family knowledge

Finally, this information needs to be treated with caution, and it is hoped that if the referral centre is unsure, then no definite sex or rearing has already been given.

*Referral*

Once it is determined that the infant needs to be referred, the receiving team can advise on the next steps to undertake before the baby can physically arrive at their hospital. An urgent karyotype needs to be performed (16) marked urgent, but blood can also be sent for FISH analysis (fluorescence in-situ hybridization); this is a test that can look for specific genetic material and, in this case, X and Y specific DNA (17). The results of these can usually be received relatively quickly, and can indicate if there is Y specific material present. Daily monitoring of the baby is advised for serum urea and electrolytes and blood glucose. After the baby is 3 days old, then cortisol and ACTH levels can be recorded, plus also 17-hydroxyprogesterone (17-OHP). Samples taken before this can potentially be abnormal (7). 17-OHP is a steroid hormone which would be raised in cases of CAH (congenital adrenal hyperplasia) (***See Chapter on CAH***)

*Assessment*

Next, the baby should be admitted to the specialist centre, for a full day admission. This would include meeting members of the multidisciplinary team (MDT) who could be involved. Further clinical assessment would need to take place, including: further endocrine investigations, possibly further and more detailed imaging, such as a pelvic and abdominal ultrasound to explore internal structures, and further blood tests looking at testosterone levels, anti-mullerian hormone (AMH) (or mullerian inhibiting substance – MIS), Inhibin B, gonadotrophins, and also urinalysis. AMH is detected in boys, and is expressed in the sertoli cells in the embryological phases of testicular differentiation (12), and Inhibin B also is produced in the testes.

Including the MDT is paramount, and the family should meet the paediatric endocrine nurse specialist (PENS), the paediatric endocrinologist, the paediatric urologist and the psychologist, for optimum and sensitive management on this first day of meeting. The team need to work together to develop a plan for immediate clinical assessment and management, exploring differential diagnoses, sex of rearing / gender assignment, and treatment, ensuring that the family have a good understanding. Information leaflets should be available from support groups, and it is recommended to offer them with full explanations.

*Diagnosis*

Further investigations may need to be undertaken once the karyotype is confirmed to confirm the actual diagnosis. If 46, XX, a short synacthen test and a urine steroid profile is needed to be performed to confirm CAH (18). If 46, XY, an HCG (human chorionic gonadotrophin) stimulation test should be performed, which is used to test the ability of any testes present to produce testosterone (19) (see Box 4.2 below (18) ) Good testicular function is indicated if testosterone rises above 5nmol/L.

**INSERT Box 4.2. The HCG test** (18)

If the chromosomes are ‘mixed sex’, or 45, X / 46, XY, then further investigations similar for Turner syndrome (***See chapter on Turner syndrome***) need to be carried out, such as thyroid function, a cardiac echocardiograph, audiology and Turner screening. In cases of 46, XX and 45, X / 46, XY, early examinations under anaesthetic and / or laparoscopy for inspection of internal structures may be necessary, or genitograms to determine any merging between the vagina and urethra (7), although these investigations are only needed if the diagnosis is proving difficult (12).

*Management*

The decision of sex or rearing / gender assignment can, usually, be made at the end of the day of the admission, which is important for parents, as the need and desire to want to register the baby’s birth with the ‘correct’ sex is important. The baby can be discharged either back to the referring hospital or home if appropriate. Full details have to be given for any immediate medical management, and education on any sick day and emergency management if the baby is 46, XX CAH, and the PENS’ role here is paramount ***(See Chapter on CAH / adrenal emergency management)***. Further management and support is given, follow up clinic appointments for the appropriate members of the MDT should be mae, and details of support groups given and explained (12).

***Adolescents***

A small group of DSD can present in adolescence, and can present in one of three ways:

1 –A girl presenting with primary amenorrhea (where menstruation has not yet commenced), with or without any breast development

2 – A girl who begins to virilise at puberty

3 – A boy with delayed puberty

*Primary amenorrhea*

A full history needs to be taken, including a family history, and full pubertal assessment (***See Chapter on puberty)*** Further investigations are detailed in the UK guidance (12) but are also outlined in Figure 4.6 (INSERT). A 46, XX disorder of mullerian development would include Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, as this is where the vagina and womb may be underdeveloped or absent (***See chapter on female reproduction)***. Whichever cause, the management of girls presenting with primary amenorrhea should be referred to the gynaecology team.

*Girls with virilisation*

Girls presenting with hirsutism and cliteromegaly is usually indicative of two possible DSD: 5 alpha reductase deficiency (5αRD), and 17β hydroxysteroid dehydrogenase type 3 deficiency, which is a condition where testosterone is not synthesized properly.

*Boys with delayed puberty*

Most boys presenting with delayed puberty are classified as having ‘constitutional delay’ (7), but other avenues need to be explored and investigated. Testosterone and gonadotrophins need to be measured; if the gonadotrophins are raised, a karyotype should be taken to exclude Klinefelter Syndrome (47, XXY) ***(See Chapter on Klinefelter syndrome)*** and 45,X / 46, XY mosaicism (12).

**4.5. 46, XX DSD**

As seen in the initial classification system (4). 46, XX DSD can encompass disorders of ovarian development, androgen excess and other disorders.

***Androgen excess***

More than 50% of all babies born with ambiguous genitalia are 46,XX (20) and this is due to the female foetus being exposed to too many male androgens (21). The appearance of the external genitalia can vary in degrees of virilisation, and this can be seen in the Prader virilisation rating scale (Figure 4.3). The source of the androgens can be testicular (20): one in every 20,000 men have a 46, XX karyotype, and this is due to a translocation of the SRY gene off the tip of the Y chromosome onto one of the X chromosomes. Phenotypically, these men may be similar to men with Klinefelter syndrome. However, the cause of the androgens is usually adrenal, and CAH is the most common cause for this (6). The majority of these children are assigned as female when they present in the newborn era. (1) (***See Chapter on CAH).***

Aromatase deficiencies are also a less common type of enzyme defect, and sometimes the cause may be due to something the mother has ingested, or maternal androgen secreting tumours. (20)

***Disorders of Ovarian Development***

This can include 46, XX ovotesticular DSD, which used to be classified as ‘true hermaphroditism’ (6). These individuals have both ovarian and testicular tissue present and will present in the neonatal period with ambiguous genitalia, and continue with virilisation at puberty. If female sex was assigned, then they may need an orchidectomy, whilst a male may need an orchidopexy. (6) The phenotype can vary, however, but often the testis is on one side (usually the right), and the ovotestis or ovary would tend to be on the left, and it is the ovary that is more likely to function. (8)

***Other causes***

Other causes for 46, XX DSD exist, such as disorders of mullerian development; ovarian function is usually normal (12), but other physical presentations may manifest, including cloacal dystrophy, vaginal atresia, or MURCS (mullerian duct aplasia renal agenesis cervicothoracic somite dysplasia) (4)

**4.6. 46, XY DSD**

Conversely, 46, XY DSD is where the child has 46, XY chromosomes, but the internal and / or external reproductive system has not developed properly in what should be expected as male. (2) It can be due to an interruption in any part of testicular development, abnormal androgen action, or other reasons.

***Clinical Presentation***

There is a varying amount of possible ways a child with 46, XY DSD can present. They may possess male internal organs (such as epididymides or vas deferens) but external genitalia may be under-masculinised, which can include a small penis resembling a clitoris, or unfused scrotum, which can look like labia. Testes may not have descended into the scrotum (See Figure 4.5 on how to clinically assess), and the urinary opening may be at the base of the phallus instead of expected at the tip, which could indicate, for example, severe hypospadias (see Figure 4.4) (2). Children can therefore present with ambiguous genitalia at birth, no development of secondary sex characteristics in a boy, or primary amenorrhea in an adolescent girl (22). The reasons why the clinical presentation can vary so much is due to how much androgen production is affected, and also where this specifically occurs within the stages of testicular development.

***Incidence***

Due to the varying clinical presentations, the actual incidence is unknown, although it is estimated that hypospadias occurs in approximately 1 in every 125 male births (22), and complete androgen insensitivity syndrome (CAIS) is known to occur in 1 in every 20,000 births.

***Tumour risk***

There is a risk of gonadal germ cell cancer in children with 46, XY DSD, and needs to be explored sensitively. This can occur because there is a higher incidence of germ cell tumours in testes that have not developed properly, and Y chromosome material is present. (22) The risk varies in the specific 46, XY DSD condition, (4) and management can vary, whether it is close observation with regular endocrine clinic follow up, biopsy, irradiation, or even a full gonadectomy (4). This remains controversial, and recent guidelines state that gonadectomy is not necessary before puberty for children with androgen insensitivity syndrome (17). Gonadectomy, however, in partial androgen insensitivity syndrome (PAIS), is dependent on the sex of rearing.

***Disorders of testicular development***

In complete gonadal dysgenesis (or Swyer syndrome), children will look typically female, but have intra-abdominal ‘streak’ gonads, and will have some risk of potential tumour development. Streak gonads mean that the gonads (either testes or ovaries) are underdeveloped and do not function, and are mainly made from fibrous tissue. In this instance, testes have not formed at all, or were ‘lost’ in early foetal development. Due to the lack of testes, there is therefore a lack of AMH, thereby resulting in external female looking genitalia, and also internal female reproductive structures (womb and fallopian tubes), but no ovaries (2). The child with complex gonadal dysgenesis may be diagnosed if a girl presents with delayed puberty, and a routine karyotype has been performed. (22)

In contrast, in 46, XY partial or mixed gonadal dysgenesis, clinical presentation can vary, as there has been some degree of testicular development, so clitoromegaly may occur, ambiguous genitalia, or a very severe hypospadias (23). The internal mullerian structures may or may not be present, and the testes can also vary in size and positioning. (24) Mixed gonadal dysgenesis signifies some degree of asymmetry in gonadal development, where there may be a ‘dysgenetic’ testis on one side, and a streak gonad on the other (22).

***46, XY DSD due to defects in androgen synthesis or action***

There are four sub-categories that come under this specific classification: disorders of AMH and AMH receptors, luteinizing hormone (LH) receptor defects, androgen biosynthesis defects, and defects in androgen action.

*Disorders of AMH and AMH receptors*

Gene mutations can occur which encode AMH or its’ receptor, and can lead to Persistent Mullerian Duct Syndrome (22), which means that mullerian duct derivatives (i.e. a small womb and/or upper part of the vagina and fallopian tubes) are present, because of the lack of action of AMH in foetal development. Phenotypically, the children will look male, but with cryptorchidism (absence of testes in the scrotum), and can present with herniation of the womb in the inguinal canal. A laparascopic hysterectomy may need to be performed, as well as orchidopexy (surgery to bring the testes down into the scrotum.)

*LH receptor defects*

These conditions are more rare, and consist of where LH receptor gene mutations have been identified that have an effect on LH receptor proteins, leading to leydig cell hypoplasia (12), which means the leydig cells in the testes (which make testosterone if LH is present), are underdeveloped. Children may present with micropenis, hypospadias and a bifid scrotum (a deep cleft in the middle of the scrotum caused by incomplete labioscrotal fusion), leading to external genitalia to resemble a phenotypical female.

*Androgen biosynthesis defects*

Testosterone is metabolized by DHT, by an enzyme called 5 alpha reductase. If a child does not have enough of this enzyme, then DHT is not produced, therefore having an overall effect on male development, resulting in a condition called 5 alpha reductase deficiency (5αRD). Phenotypically, children present with external female genitalia at birth, but will also have testes in the inguinal region, and internal male reproductive structures (25). Most children are reared as females, and may undergo gonadectomy. However, if they have not had the surgery by the time they reach puberty, they will begin to virilise: their voices deepen, their phalluses enlarge, but they do not develop any facial or body hair, or acne. At puberty, these children may change their gender to male (26), and undergo testosterone replacement therapy, or use DHT cream (25). However, some may remain as females, and the subsequently undergo gonadectomy, vaginoplasty, and treatment with oestrogen therapy (27).

*Defects in androgen action*

If androgen receptors do not function properly, then the result may be varying degrees of androgen insensitivity, i.e. a lack of androgen response, and therefore incomplete virilisation in a person with 46, XY make-up.

Complete Androgen Insensitivity Syndrome (CAIS)

CAIS is where a child is 46, XY, but is completely phenotypically female, and has intact testes. Clinical presentation may manifest in infancy, with inguinal hernia or labial swelling (containing the testes), which is rare (28), or in adolescence, when the adolescent presents to clinic with primary amenorrhea. She will have developed breasts, with a female body shape, which is due to increased oestrogen production by the aromatization of androgens. The testes in the inguinal area, if they have not been removed, may be uncomfortable (29), but the risk of malignancy is significantly lower after puberty, although lifelong surveillance is advised. To date, the topic of prophylactic gonadectomy in girls with CAIS is still very controversial (24)

Sex of rearing in CAIS is female, and the girls retain a female gender identity (30), with the girls tending to be satisfied with their sexual functioning in adult life, although this is dependent upon vaginal lengths and any previous surgeries (31).

Partial Androgen Insensitivity Syndrome

Whereas gene mutations in androgen receptors are identified in more than 95% of women with CAIS, mutations are less common in PAIS (32), and the phenotype depends on the severity of the androgen receptor dysfunction, and amount of androgen insensitivity. (30) However, there is usually some degree of genital ambiguity, and underdevelopment of the penis, severe hypospadias, and a bifid scrotum, which may contain gonads (28). Parental decisions on sex of rearing can be either as a boy or a girl, depending on the size of the phallus. If female, the testes may be removed to remove the possibility of changes due to testosterone, and again, the risk of germ cell tumours (29), and the malignancy risk varies, depending on the location of the testes. If raised as male, then regular surveillance of the testes is essential, and recent data has shown that children with PAIS are raised as male (30), although breast development can occur at puberty. There may be a degree of gender dysphoria in adulthood, but again, this is dependent on phallus size and sex assignment at birth. (24)

**4.7. Mixed Sex Chromosome DSD**

Mixed sex chromosome DSD occurs when there is aneuploidy – ie, an abnormal number of chromosomes, and can be relatively common (47, XXX, 47, XXY, 45, X or 47, XYY) or part of a mosaic karyotype (8). This is where one kind of karyotype is present in some cells, and a different karyotype in other cells, for example, 45, X / 46, XY.

***45, X / 46, XY***

This is the most common karyotype which is linked with ambiguous genitalia, with CAH and AIS. The anatomy in affected children can result from gonadal dysgenesis, ie, maldeveloped gonads. Where one gonad is *streak*, and the other is *dysgenetic*, the child is said to have *mixed gonadal dysgenesis*, so asymmetrical gonadal development (10, 29).

Children can present differently and have a varied phenotype, but those presenting with a male phenotype tend to be shorted and have dysgenetic testes (8). However, individuals with a female phenotype may have features similar to Turner syndrome, and most have short stature. They can present ante-natally, at birth with ambiguous genitalia, or later in adolescence with short stature or delayed puberty, or even in the oncology setting with a germ cell tumour (29). Due to this, it has been argued that gonadectomy should be performed in infancy if the child is to be reared as a female. If male, the testes need to be observed regularly with serum tumour markers, and potentially biopsy after puberty. Sex of rearing is dependant on the external genitalia phenotype.

***46, XX / 46, XY DSD***

This is a chimeric genetic disorder, i.e., where a cell can be made up of different zygotes, and can be referred to as chromosomal ovotesticular DSD. Because of this mixed sex chromosome, both ovarian and testicular tissues are found in either the same gonad, or the opposite gonad, just as in 46, XX ovotesticular DSD, or 46, XY ovotesticular DSD. The distribution amongst the gonads vary, but both ovarian follicles and seminiferous tubules are present.

Some women with ovotesticular DSD have become mothers, but not ovotesticular DSD males have become fathers (8), so it is clear that the ovary is dominant. If testicular tissue is not removed, then re-evaluation of endocrine status is essential at the time of puberty.

***Klinefelter syndrome – 47, XXY (See chapter on Klinefelter syndrome)***

Klinefelter syndrome results from two or more X chromosomes in males. Symptoms can vary, and sometimes diagnosis is made when the adult male has investigations into infertility, due to high FSH and LH levels (8). There is decreased testicular function in most affected individuals, so smaller testes are present, and sometimes there may be some degree of learning difficulty (10)

***Turner syndrome – Monosomy X or 45, X or 45, XO (See chapter on Turner syndrome)***

Part or all of one of the X chromosomes is missing in Turner syndrome (TS). Girls with TS do not tend to come under the ‘DSD’ classification in clinical practice, but it sits within the consensus nomenclature, and many endocrine centres internationally will have their own TS clinics. There is a characteristic phenotype for girls with TS, including short stature and gonadl dysgenesis. Phenotypically, the girl with TS will also have female external genitalia. Diagnosis can be made antenatally, in infancy, in childhood where slow growth is noted, or adolescence, where the girl presents with delayed puberty and amenorrhea.

**4.8. Management**

***Medical management***

It is common sense that the baby born with ambiguous genitalia needs urgent medical evaluation, including a thorough newborn physical examination (33), specifically looking for any dysmorphic features (34). Urgent blood samples, as previously stated, need to be performed, as well as clinical monitoring in the immediate newborn period. If a diagnosis of salt wasting CAH is made, then commencing hydrocortisone and fludrocortisone is paramount, as well as salt replacement, ***(See Chapter on CAH)*** in order to prevent an adrenal crisis.

Hormone replacement therapy is needed in all females with mixed gonadal dysgenesis, or in genotypic males who have either had their testes removed, or where they experience testicular failure. (34)

***Surgical management***

Surgical management of the child with a DSD remains controversial. Reconstructive surgery is performed for cosmetic reasons, to allow vaginal-penile intercourse, and to be able to achieve a ‘sex-typical’ manner for urination (ie for males to be able to stand whilst urinating) (35). The controversy lies behind *if* to perform surgery, and *when.* Early infancy surgery is advocated by some as the procedure is easier, and that there is also less stigma for the family. However, adults who have undergone surgery in this period are not happy with sexual function and satisfaction. (35) Feminizing genitplasty (clitoroplasty, vaginoplasty and sometimes labioplasty) is only performed in the most severe cases of virilisation (Prader 3 – 5) (36), with an emphasis on preservation of erectile function and not cosmetic appearance being of upmost importance. The whole multidisciplinary team, alongside the parents, must be involved in decision making for this aspect of care, although guidelines do state to leave or delay for as long as possible (17).

Gonadectomies in under-virilised 46, XY DSD males also remain controversial as stated, and also in individuals with mixed sex chromosome DSD, where the gender identity may vary. (37)

***Psychosocial management***

Whilst it is important to focus on the physical aspects of a DSD, it cannot be underestimated that a vast input from psychological services is paramount. (17) Support for the parents with a newborn with ambiguous genitalia is essential, as is support for the child and adolescent, irrespective of when a diagnosis is made. A psychologist can help the family with decisions regarding sex of rearing, timing of any surgery, and possible sex hormone replacement (38). Assistance can also be given in how best to tell friends and family on their child’s diagnosis, and possible change of sex, especially if they were told something different antenatally (39).

Support and guidance should be maintained as the child grows and develops, with caution given if there are any questions regarding gender identity. Gender role behaviour can be atypical in children with a DSD, but this is not necessarily an indicator for definitive gender re-assignment (36). Nevertheless, gender dysphoria can remain an issue (29), especially in adults who may have had surgery as an infant / child, with an unsatisfactory outcome.

Psychological input is also necessary when contemplating diagnosis disclosure to the child or young person, regarding karyotype, gonadal status, and possible future fertility, and it is advised that acceptability and psychosocial adaptation is helped with honest disclosure (17). The psychologist can work closely with the family on this, helping the child and family with counselling and guidance for an optimum quality of life.

**4.9. The Multidisciplinary team (MDT)**

It is clear that the management of the child with a DSD, and their family, must take a full multi-disciplinary approach (17). Children with a DSD must be able to access centres of excellence which are fully equipped, manned and experienced in dealing with DSD, and have a full team ready. An integrated team approach can be seen in Figure 4.7. (36, 40) (INSERT)

***The Psychologist***

This team member is so important, and must be available to the child / young person and family from the very beginning (41). The diagnosis of a DSD can be unexpected and overwhelming, and, as discussed, advice and guidance can be given in how to verbalise concerns, how to deal with emerging emotions, and how to guide their child / young person in how to develop alongside their peers. Some families express the need to be in touch with other families experiencing the same, or similar, diagnosis (42). Feelings of isolation or stigmatization can be reduced if the family feels they are not alone. Patient support groups can provide a valuable service to families, providing clear guidance and advice from other families ***(See Section 4.12)***

***The Paediatric Endocrinologist***

The Paediatric Endocrinologist will play a major role in the child’s management and decision making of any clinical investigations to be performed (40). They are often the first port of call when receiving a baby with ambiguous genitalia. As 46, XX CAH is the most common DSD (29), management and education on adrenal crises, replacement and other medication needs to be co-ordinated by a paediatric endocrine team. Further on, as the child grows, clinical monitoring may be necessary, with regards to hydrocortisone replacement and compliance, mineralocorticoid dosing and salt supplementation (43), as well as growth monitoring and pubertal management, especially in individuals with non-functioning gonads (36). In addition, Gonadotrophin releasing hormone (GnRH) therapy may be required in young people where gender identity is uncertain, and also growth hormone therapy and oestrogen in girls with Turner syndrome.

***The Paediatric Urologist / Surgeon***

The Paediatric Urologist also plays a key role. A joint meeting with the Paediatric Endocrinologist and family is ideal, so as to physically assess and clinically examine the baby with ambiguous genitalia together. As well as the external genitalia, the Urologist should be able to palpate / locate the gonads. If any cosmetic surgery is to occur, it should be this experienced surgeon who deems it necessary, and is confident in the eventual function and acceptable cosmetic appearance. Hypospadias repair also comes under their remit, and also the need for gonadectomy if the risk of malignancy is high (40).

***The Paediatric Endocrine Nurse Specialist (PENS)***

The role of the nurse specialist has been advancing in specialist DSD services (44). The PENS is key in just as a support for the child and family, but for liaising with the MDT, organising investigations (12), and ensuring smooth running and organisation of MDT clinical meetings. Much has been written on the role of the Clinical Nurse Specialist ***(See CNS role chapter)*** but the PENS multifaceted role can be seen in Figure 4.8. (INSERT) It can be highlighted here that the role of the patient advocate is at the forefront of the multifaceted role. Families will often have the PENS’ contact details and contact them directly with any queries or concerns, rather than waiting for their clinic appointment.

***Other MDT members***

Although the healthcare professionals discussed are key ***(See Box 4.3.)***, other team members play an important role in the care and management of a child with a DSD.

**INSERT Box 4.3. The MD**T

Gynaecologists can be available when the child is an infant to advise on potential outcome of any interventions, and advise on pubertal management in girls (40). Biochemists can ensure swift management of expedited samples arriving in the laboratory, and provide guidance on the investigation to be performed (12), likewise with Genetics services. Ethicists, cultural and religious leaders can also not be discounted, and conflicts may arise, and ultimately clinical experts need to act in the best interests for the child (40). Ethical principles need to focus on the following: (41)

1 – Minimizing physical risks

2 – Minimizing psychological risks

3 – Preserving potential fertility

4 – Preserving the ability to have satisfactory sexual relationships

5 – Respecting parental desires and beliefs

Respecting parental beliefs do need to be considered: for some, a DSD may still have a stigma, and social, religious and cultural factors may play an important role when deciding on gender roles and gender assignment, especially in 5αRD. Religious leaders may also be able to offer the family continuing support.

Local teams need to be included, such as the local Paediatrician, General Practitioner (GP), or Health Visitors, who again can provide ongoing support to families. Links must be made with the GP who may be responsible for repeat medical prescriptions, and arrangements to be made with the local Paediatrician for immediate paediatric ward access if the child suffers and adrenal crisis. Community nursing teams can also offer assistance in obtaining serum sodium samples in infancy if need be, plus GnRH analogue therapy or testosterone injections where necessary during adolescence. Multidisciplinary team work is essential all round to achieve the desired goals for the child and their family.

**4.10. Nursing Considerations**

***At diagnosis***

PENS need to be aware from the beginning how to approach families who’s child has been diagnosed with a DSD. Using ‘medicalized’ language can be daunting and confusing for parents (45), so great care needs to be taken in using understanding terminology. Supporting literature is paramount, especially regarding how to cut up tablets, when to administer and how, or administering salt supplements, if the child has 46, XX CAH, plus also sick day and emergency management advice ***(See Chapter on CAH)***. Practicalities to consider for the initial meeting with the MDT during the first admission need to be considered, and can be seen in Box 4.4.

**INSERT BOX 4.4 Admission practicalities to consider**

The PENS can make contact with the family prior to the admission and explain the need for the practicalities outlined. Babies with ambiguous genitalia should begin their diagnostic pathway as soon as possible, usually within the first five days of life, so the PENS must be sensitive with the family who are going through an emotional upheaval regarding a potential diagnosis, notwithstanding having just given birth. The day of admission can be lengthy; as arrangements are usually made at short notice, the need for waiting times between visits from the MDT need to be explained, as they may be holding a clinic or in surgery, so their times need to be co-ordinated carefully. The PENS can act as an advocate and liaison for the family during the admission, enabling potential stressful situations to be eased, and being able to answer questions with non-medical jargon (46).

***Ongoing management***

Prior to discharge, the PENS needs to ensure that the family have a full understanding of the condition, and can offer further, less formal appointments with him/herself to continue with education and support. Again, the role of support groups and perhaps local families cannot be underestimated. Ongoing management in outpatient clinics will be dependent on the specific DSD, but the PENS is the ideal healthcare professional to offer continuing support. Regular MDT meetings can be held monthly and provide updates to healthcare professionals on any emerging issues seen in the outpatient clinic.

***Transition and beyond***

Management in adult services is very different to the paediatric world, and it is essential that a seamless transition, and not a simple transfer of care, is enabled ***(See Chapter on Transition)*** Long term studies and data in young adults with DSD is still lacking (47), but continued engagement with members of the MDY should be encouraged when meeting with adult services. Continued attendance can also provide healthcare professionals with valuable long-term data in order to be able to provide the best care in future generations of young people with a DSD.

For those young people with a DSD, if not diagnosed in infancy, the diagnosis may have been made recently, so their relationship with paediatric services may have been relatively short, if at all. Issues concerning genital examinations, gonadectomy, disclosure and psychological issues need to be fully explored and appreciated (47), with full realisation that ‘the patient’ is now ‘the adult’, and all decisions to be made will now transfer to them (48). The MDT relationship, however, must not stop, and the journey should continue.

**4.11. Conclusion**

For children and young people with a DSD, and their families, diagnosis and further management can conjure up a great deal of uncertainty and confusion. Paediatric endocrine nurses need to have a good understanding regarding not just the aetiology and clinical aspects of the different DSD, but also the emotional and psychological impact that a diagnosis of a DSD can have. International consensus guidelines (4) have been formulated, and a new classification system has been formed, which has formed the framework of this chapter. Whilst the most common DSD have been discussed, the umbrella of DSD is vast, and not all conditions have been covered here. The emphasis, however, is on the full MDT working with and alongside the child and their family. The PENS needs to consider their multifaceted role and engage in the roles of not just ‘clinical expert’, but also as ‘patient advocate’ and ‘liaison’. Parents want their child to live as ‘normal’ a life as possible (46), and it is with the information and guidance from the PENS and the MDT that can hopefully enable seamless transition from diagnosis and beyond.

**4.12 Useful websites**

[www.dsdfamilies.org](http://www.dsdfamilies.org) UK DSD support group

[www.dsdteens.org](http://www.dsdteens.org) UK DSD young persons support group

[www.aissg.org](http://www.aissg.org) UK Androgen Insensitivity Syndrome support group

[www.aisdsd.org](http://www.aisdsd.org) USA AIS support group for women and families

[www.accordalliance.org](http://www.accordalliance.org) International information page for healthcare professionals and families

[www.heainfo.org](http://www.heainfo.org) USA Hypospadias and Epispadias Association

[www.hypospadiasuk.co.uk](http://www.hypospadiasuk.co.uk) UK Hypospadias support group

[www.livingwithcah.com](http://www.livingwithcah.com) UK CAH support group

[www.tss.org.uk](http://www.tss.org.uk) UK Turner Syndrome support group

[www.turnersyndrome.org](http://www.turnersyndrome.org) USA Turner Syndrome support group

[www.ksa-uk.co.uk](http://www.ksa-uk.co.uk). UK Klinefelter Syndrome support group

[www.genetic.org](http://www.genetic.org) USA Klinefelter Syndrome support group

[www.livingmrkh.org.uk](http://www.livingmrkh.org.uk) UK MRKH support group

[www.MRKH.org](http://www.MRKH.org) USA MRKH support group

[www.verity-pcos.org.uk](http://www.verity-pcos.org.uk) UK PCOS support group

[www.isna.org](http://www.isna.org) USA Intersex Society of North America

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