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Management of disorders of sex development – With a focus on development of the child and adolescent through the pubertal years

Jamal Raza, Director, Prof. and Head of Department, Pediatric Endocrinology [a, *],
Syed Zafar Zaidi, Professor of Pediatric Urology [b],
Garry L. Warne, Professorial Fellow [c]

[a] National Institute of Child Health, Rafiquee Shaheed Road, Karachi, 755001, Pakistan
[b] Dean Indus University of Health Sciences, The Indus Hospital, Karachi, Pakistan
[c] Department of Paediatrics, Faculty of Medicine and Health Sciences, University of Melbourne, Melbourne, Australia

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Disorders of sex development, congenital conditions in which chromosomal, gonadal or anatomic sex is atypical at birth, require urgent assessment by a multidisciplinary team, to define whether there is a life threatening disorder of congenital adrenal hyperplasia or a healthy child with a complex condition. Uncertainty, stigma and taboo complicate counselling which must be knowledgeable, comprehensive and sensitive to different circumstances, religions and cultures. This articles will discuss clinical and genetic diagnosis, decisions regarding sex of rearing, ethical dilemmas, medical management of the infant and of the child or adolescent presenting for the first time with a DSD. Surgical options, timing and management are outlined.

* Corresponding author. Fax: +9299205368.
E-mail addresses: drjamalraza@gmail.com (J. Raza), zafar.zaidi@gmail.com (S.Z. Zaidi), garry.warne@rch.org.au (G.L. Warne).

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Introduction

At the Chicago Consensus meeting in 2005, disorders of sex development (DSD) were defined as congenital conditions in which chromosomal, gonadal or anatomic sex is atypical at birth [1] Since then many aspects of management have undergone change. In this article we will review updates in each area along with limitations in resource-limited countries, including those related to local cultural realities.

Although the main focus of this series of articles is puberty, it is impossible to consider DSD in puberty in isolation from what may have occurred before, during infancy or childhood, since decisions made then have long term reverberations that continue throughout adult life.

Nomenclature

Some of the nomenclature has changed since the Chicago conference. The umbrella term of "DSD" is still the one preferred within the medical profession, but some advocacy groups see the term 'disorders' as offensive and assert that 'differences' or 'variations' of sex development would be more acceptable terms. The older term 'intersex', which was discarded at the Chicago meeting, has been reclaimed by many advocacy groups and is now being used again, although the parents of girls with congenital adrenal hyperplasia do not accept it [2]. Terms such as hermaphroditism and pseudohermaphroditism are no longer acceptable. In this review, for the sake of clarity we will use the terminology that was agreed on at the Chicago conference, but acknowledge that it may need to change. We will refer to 'sex development' as the process by which the external genitalia and internal reproductive organs develop and 'sex differentiation' as the process by which the undifferentiated gonad develops into an ovary or a testis.

Management is complex

Disorders of sex development comprise a wide range of underlying disorders with diverse clinical features and modes of presentation.

They may be recognized soon after birth due to ambiguity of the external genitalia or remain hidden until the second or third decade, as in the case of complete androgen insensitivity, in which a girl with breasts and no pubic hair may be found to have a 46,XY karyotype, testes and no uterus. These variations pose a big challenge to clinicians and management plans need to be carefully developed on a case by case basis. The needs of a child with DSD going through puberty will be different if the diagnosis was made soon after birth due to genital ambiguity, rather than having been made much later on other grounds. In the former, actions taken in the first few months of life, including genital surgery, will have shaped the child's future. Additionally, the parents would have had to cope with very stressful experiences, including participating in decisions about the child's sex of rearing and about surgery. Alternatively, the child may have appeared normal at birth may then have been discovered later in childhood, adolescence or even adult life to have internal anatomy at odds with the genital sex. The example of complete androgen insensitivity has been mentioned, but there are also girls who do not enter puberty at all because they have complete gonadal dysgenesis. Their health could be threatened because of the very real risk of gonadal cancer. In each case, the child and the parents have to deal with the shock of discovering that the future is not going to be as they thought it would be. Profound questions about gender identity, sexuality and fertility will be asked and need to be addressed.

By definition, the *anatomy* of the reproductive tract in a person with DSD is neither typical male nor typical female anatomy.

When the *external* genitalia are atypical in appearance, such that the phallus is smaller than a typical penis and larger than a typical clitoris, and the labio-scrotal folds are partially fused, there will be uncertainty about the child's sex. Naming the child may present difficulties. The parents may find telling relatives and friends about the baby distressing to the extent that they avoid saying anything and isolate themselves from support. In the absence of any surgery, the child growing up with atypical genitalia could be the target of rumour and discrimination, which could also be directed at the child's family. During adolescence, sexual function and menstruation could be affected. In adult life, fertility

might not be possible. If the *gonads* have not fully differentiated, as in 45,X/46,XY partial gonadal dysgenesis, there is a markedly increased risk of gonadal cancer. Premalignant gonadoblastoma cells may be present in the testes at birth and can develop into malignant seminoma during childhood, adolescence or adult life. In addition, if the decision is to retain the testes, they may secrete testosterone at puberty and further masculinize the external genitalia and perhaps cause gender identity to become more masculine. This may or may not be desired. In some cases of Y-chromosome positive gonadal dysgenesis, a *uterus* is present, allowing for the theoretical possibility of a pregnancy, perhaps with donated gametes. In many types of DSD, the anatomy of the *lower urinary tract* is also atypical. The urethra may open into a urogenital sinus, with risk of ascending infection.

All of these different anatomical, developmental, psychological and social aspects must be considered from the outset when deciding how best to treat the child and this is why the field is so complex. Deciding whether the child should be raised male or female is not always an easy matter. A team approach to decision making, in consultation with the parents, is highly recommended.

A multidisciplinary team to deal with complexity

Initially mentioned in the consensus article, and in subsequent guidelines [3], the optimal care for infants and adolescents with DSD requires support and functioning of a multi-disciplinary team. The composition of the team will vary from country to country, depending on the availability of the various disciplines identified.

- In most cases, a neonatologist or general paediatrician is the first point of contact for parents. He or she reveals existence of such a condition and often orders the first set of investigations for the baby.
- From then on, a paediatric endocrinologist or person with a special interest in the field takes a pivotal role, around which other members of the team revolve.
- The other very crucial member of the team is the paediatric surgeon, preferably a paediatric urologist, as subsequent management mostly has a surgical component attached to it [4].
- Ideally, the team would also include a mental health professional and/or a social worker with special training in the area of DSD.
- In many centres, a gynaecologist specialized in dealing with adolescent patients (many of whom are female) would provide surgical services to teenage girls and young women with DSD.

Counselling

It is imperative that from the start both parents are involved in all the discussions. Starting from the first point of contact, all members of the team should be very careful to avoid confusing the parents by expressing differing opinions or using inappropriate terminology. It is better to refer to the infant in talking to them as “your baby” than as “it”. The information to be given to the parents should build on what is already known or has been discussed. The number of team members to be involved in discussion with the parents should be kept to a minimum and each member should have a clear understanding of how that family may have previously thought about these conditions (if they had heard of them at all) and of their religious background, since these will need to be addressed when planning counselling and subsequent management. All cultural connotations must be understood well. Discussion should be undertaken in a manner completely understandable for the parents, using simple, non-technical terms. The parents may need to hear explanations several times before they fully understand what is being said and they may benefit from discussing what the doctor said with another health professional, such as a psychologist or social worker. It is always important to document the information that was given and the key points raised in discussion in the patient's record. This is to avoid duplication and also to let other team members know what has already been discussed and explained to parents.

In the event of first presentation occurring in older child or adolescent, the young person should be part of the discussion from the beginning and as far as possible be in control of subsequent decision making.

There is often a lot of shame, uncertainty, stigma and taboo attached to disorders of sex development, with differences depending on the local culture. In the Indian sub-continent, fear of a child being born as a 'Hijra' (an extremely derogatory label attached to eunuchs, intersex and transgender people) may be so great that parents may be willing to give their child away for others to raise [5]. In some cultures, it is a common belief that the birth of a child with a DSD is a punishment for a mother who has sinned, or that the disorder results from some black magic. This can lead to the mother being ostracized or even physically attacked. Families therefore need a lot of support throughout the process of management especially during the early days when the diagnosis is uncertain.

Diagnosing the conditions that cause dsd

Scenario 1. An infant with ambiguous genitalia

The starting point in assessing an infant with ambiguous genitalia is to remember that there are *two common diagnoses* and a number of rare conditions which account for the remaining small number.

The two *common* diagnoses are congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (in which case the child will be genetically female), and 45,X/46,XY partial (or mixed) gonadal dysgenesis (MGD).

CAH

Salt-losing CAH is a *life-threatening* condition. It should therefore be assumed that this is the diagnosis until proved otherwise. Clinical features that would support a diagnosis of CAH are: genital hyperpigmentation (due to an increase in ACTH); absence of palpable gonads; any evidence of a metabolic disorder (systemic illness, vomiting, dehydration, hypoglycaemia); and a positive family history of affected siblings. The diagnosis would be confirmed by finding a low serum sodium, a high serum potassium and an extremely high serum 17-hydroxyprogesterone. Treatment with hydrocortisone, iv fluid, electrolytes and glucose could start immediately. Other investigations would be done to define the anatomy of the urogenital sinus and to confirm the presence of uterus and ovaries. The chromosomes should be 46,XX.

MGD

An infant with 45,X/46,XY partial gonadal dysgenesis will usually have at least one palpable gonad (which will nearly always be a testis) in the inguinal canal or labio-scrotal fold. The hyperpigmentation and metabolic disorders associated with CAH are absent. Pelvic ultrasound will only very rarely show a uterus to be present. The infant might show some dysmorphic facial features similar to Turner syndrome. The diagnosis would be made on the chromosome analysis of 50–100 cells or by DNA microarray, which is being increasingly used. As dysgenetic testes are predisposed to become malignant, a management plan needs to be prepared that minimizes the risk of death from cancer. This might include the removal of intra-abdominal gonads when a Y chromosome is present and long-term monitoring of scrotal gonads that are retained.

46,XY DSD

This is not a single condition, but one with many possible genetic origins. Identifying the underlying diagnosis in infants with ambiguous genitalia and a 46,XY karyotype is notoriously difficult, but the application of advanced molecular genetics is making it possible to improve the success rate, at least in research centres. This group of conditions includes X-linked disorders of the androgen receptor and a number of recessively inherited conditions, including 5α-reductase deficiency, rare disorders of testosterone biosynthesis and rare disorders resulting in gonadal dysgenesis. A detailed description of these disorders is beyond the scope of this review. The principles of management are similar for all of them.

It is absolutely critical that either an exact underlying diagnosis is made or that one should get as close to the diagnosis as possible before embarking on a management plan. Cumbersome and complicated investigations might delay this process at times but that delay is worth the wait. The identification of a genetic mutation in one member of a family enables other members of the family to be screened. Future generations also benefit, since prenatal diagnosis becomes possible.

Presentation in early newborn period

A detailed *history and examination* is essential in all situations. Any ante-natal virilization in the mother is relevant, as is her history of drug usage or history of any tumors. Great care must be undertaken in documenting the family history, taking special note of consanguinity, history of previous neonatal deaths and a history of siblings and other family members being diagnosed with a DSD or having features suggestive of a DSD. Family members hitherto undiagnosed but with a suspicion of DSD such as unmarried or childless adults may provide useful additional information.

On *physical examination*, the presence of any dysmorphic features might suggest a chromosomal abnormality. Hypertension suggestive of either renal impairment or mineralocorticoid excess should be excluded. Genital examination should include a detailed evaluation of penile/phallic size and corporal thickness. Various methods have been used to measure stretched penile length but the penis is usually measured from pubic base to the tip when fully stretched [6]. It is also useful to use centile charts if required, as penile sizes may vary according to ethnic background. Details of where the urethral and/or vaginal openings are located should also be noted. Labioscrotal folds should be examined for texture, thickness, degree of pigmentation and possible fusion. Gonads should be carefully identified for their presence and location. When palpable, size of the gonads is also noted using an orchidometer or a ruler. One gonad is the usual finding in partial (mixed) gonadal dysgenesis, whereas an infant with ambiguous genitalia and two palpable gonads is more likely to have a defect of androgen synthesis or androgen action. If no gonads are palpable, the possibility exists that the baby is a virilized female. For the sake of some standardization, It is better to use virilization charts such as Prader scoring chart and external masculization score (EMS) [7] which make communication easy and understandable.

All these details must be thoroughly documented in notes in words and pictures for others to consult at a later stage.

Scenario 2. Later presentation

In countries with an advanced economy, DSDs characterized by ambiguous genitalia almost always receive specialized medical attention within hours or days of birth, but in resource-poor environments children with the same conditions might not be seen by any doctor for months or even years. Delay inevitably compromises outcomes and makes management more difficult. There are many reasons for a delayed presentation.

i. Sometimes excessive or even complete virilization in a genetically female child may lead to a male sex of rearing (which may be preferred for cultural reasons) and a realization may set in much later when the absence of testes is investigated.
ii. Girls with complete Androgen Insensitivity Syndrome (cAIS) have a normal female appearance and develop breasts at puberty, but fail to develop pubic hair and do not menstruate. They identify as female. Swellings in the groin (testes) are usually noticed and are the reason for bringing the child for investigation.
iii. In some situations, the genital ambiguity may not be very obvious or it is missed due to home delivery by a midwife, hence presentation may be delayed.
iv. In certain cultures, parents may be aware of ambiguity but still do not seek early medical care for reasons of taboo, preference for alternative care, or shame preventing them from bringing this out into the open. Such delay may lead to progressive virilization, with effects on phallic size, linear growth, the pitch of the child's voice, behaviour, exposure to rumour and discrimination, and psychological development.

v. The development of an intra-abdominal gonadal cancer in adult life is sometimes the first indication of an underlying DSD.

Hence, the varied presentation at different ages may present a diverse challenge for the treating physician, and to the subsequent management of the child.

Investigations

46XX DSD. The first priority is to exclude the life-threatening condition, which is salt-losing CAH. If this is not possible on clinical grounds (e.g. testes palpable), then an urgent serum 17OHP should be requested. If it is greatly elevated, further investigations (serum electrolytes, blood glucose) are done prior to and during the initiation of glucocorticoid and mineralocorticoid therapy.

After CAH has been excluded, most investigations depend on the initial karyotype, which forms the basis of classification of DSD.

45,X/46,XY DSD. Investigations are needed to define the anatomy. A pelvic ultrasound or MRI will establish whether or not a uterus is present. The type and precise location of the gonads should be established. This may involve surgical exploration including biopsy of the gonads. Streak gonads should be removed immediately as they are non-functional, contain no germ cells and represent a substantial cancer risk. Testes to be retained should be brought down to the scrotum or at least the inguinal canal where they can be monitored by palpation. A biopsy should be performed looking for gonadoblastoma. Further investigations appropriate for Turner syndrome (heart, kidneys) may be indicated.

46 XY DSD. The list of conditions forming the differential diagnosis is quite large. They are all genetic and the most expedient way of establishing the precise diagnosis is to look for the mutation using the latest molecular genetic technologies. These are not yet widely available.

Comparative Genomic Hybridization (CGH) arrays sometimes with MLPA have been extensively utilized to detect small to large-scale genomic duplications and deletions in large cohorts [8–10] a yield around 21–30% is reported Multiple parallel sequencing (MPS) involving a panel of target genes is currently the most efficient method of genetic analysis in this group of disorders despite the availability of Whole exon sequencing (WES) and Whole genomic sequencing (WGS), which are more costly options. The largest reported cohort of 278 patients using MPS and targeting 64 known candidate genes has improved the yield of genetic diagnosis to 43% [11].

More traditional endocrine investigations would always include serum FSH, LH and testosterone, and an HCG stimulation test measuring the rise in serum testosterone, (Δ4-androstenedione (Δ4A) and dihydrotestosterone (DHT). Normally a 2–3 fold rise in serum testosterone from the basal level is expected, a flat testosterone response suggesting the possibility of a testosterone biosynthetic defect (17α-hydroxylase and 17–20 lyase) or Leydig cell hypoplasia. A disturbed T:Δ4A ratio suggests 17β HSD type III deficiency, while an altered T:DHT ratio is diagnostic of 5α-reductase deficiency. Finally, an elevated basal and stimulated testosterone level is indicative of a partial androgen insensitivity syndrome. However, all these investigations often provide a suggestive diagnosis, if at all. In the majority, no definitive diagnosis is made on the basis of endocrine tests, hence all efforts should be made in trying to obtain a definitive genetic diagnosis if possible. Often a panel of common genes involved is sequenced to pick up the common diagnoses. Specialized and rare genetic tests can be performed at research centers.

Principles of management and some ethical considerations

When someone is born with the different anatomy that we call a DSD, there is never going to be a perfect outcome, with or without treatment. The aim of management is to give the person the best possible chance of freedom from illness, healthy psychosexual development, a positive sense of social wellbeing and to maximize opportunities for satisfying sexual relationships and if possible, fertility. The degree to which parental control should influence decision making about treatment options will diminish as the child becomes older and develops capacity to exercise independent consent.

Deciding the sex of rearing

Whether or not genital surgery forms part of management, every child should be given a male or female public identity and raised in ways consistent with that identity. This is to give them the best chance of happiness and social integration. Once the sex has been announced and registered, the parents should be encouraged to give the child a name consistent with that the sex that society has recognized, not a name that could be either male or female. The child's innate gender identity will eventually assert itself, but until that happens, their place in their peer group will be more secure if they are not made to feel different or unusual.

In the case of a 46,XX child with CAH, assignment to the *female* sex is straightforward because experience shows that if treated from early childhood, they almost always grow up identifying as female and have the potential to be mothers. Feminizing genitoplasty, which divides the fused labia and creates a vaginal opening separate from the urethra, enables menstruation at puberty and penetrative sexual intercourse in adult life. Clitoral reduction is often performed as part of this operation, although it is not strictly necessary for medical reasons.

The decision about sex of rearing for DSD patients born with ambiguous genitalia, other than girls with CAH, is more problematic because of the high degree of uncertainty about the long term outcome.

Genetic sex does not in itself determine gender identity, nor does the type of gonad. 46,XX females with complete androgen insensitivity have testes and high circulating levels of testosterone, but due to the lack of androgen receptors, almost always identify as female. It is also relevant to remember that gender identity is the reverse of chromosomal and genetic sex in people with gender identity dysphoria who have none of the features of a DSD.

If a child with ambiguous genitalia is born with a testis that can be retained, it will probably secrete testosterone and bring about a greater amount of masculinization over time. This may even be sufficient to give the child a male social gender and a male gender identity, attributes which might prove to be culturally and economically advantageous in certain societies. Some DSD conditions, such as 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency are well known to be associated with significant masculine development and transition to a male gender identity after the onset of puberty [12], but these conditions are rare. Mixed gonadal dysgenesis is far more common and the future gender identity is less predictable in this condition. Similarly, children with partial androgen insensitivity often identify as male. If there is a significant chance that the gender identity will be male, the removal of genital tissues, especially reduction in erectile phallic tissue, should not be contemplated and assignment to the male sex is the wiser choice because it preserves choice. If the child identifies as female in later years and wants surgery to make it possible for her to function as a female, that is her choice. Someone who has had feminizing surgery as an infant and who later identifies as male is denied that choice because tissue has been removed and that is irreversible.

Recommendations based on the underlying diagnosis

In past decades, it was believed that, regardless of the underlying diagnosis, feminizing genitoplasty would give a better long term outcome than any attempt to create male genitalia. This was on the mistaken premise that gender identity depended more on nurture (how the parents raised the child) than nature (any effect of pre- or postnatal hormone exposure). We now know that this is not true – in fact, very little is known about what determines gender identity – and have abandoned that approach. Recent large European studies have identified a higher occurrence of gender dysphoria and non-binary orientation of gender in patients with DSD [13]. We would currently make the following recommendations:

Raise female:

- In 46 XX adrenal hyperplasia, all efforts should be made to raise the child as a female to maximize her chance of fertility. This will generally be successful provided medical treatment has adequately suppressed androgen secretion throughout childhood.
- Children with CAIS are unambiguously female and the fact that they have a 46,XY karyotype and testes makes no difference to that. Their development as females was no less directed by their genes

than that of a girl with 46,XX chromosomes but the sequence of genes involved was different. Furthermore, girls with CAIS cannot respond to testosterone, which makes it pointless to tell the parents that they were meant to be boys. Adults with CAIS may feel that the absence of a uterus detracts from their ability to feel complete as women, but it does not make them less female.

Raise male:

- Mixed gonadal dysgenesis. The better differentiated testis does carry the risk of malignant change, but testicular changes threatening harm can be detected early with regular physical and if necessary, ultrasound examination. Removing a solitary testis converts a probability of infertility into a certainty and for this reason, advocacy groups are opposed to the removal of gonads. In Australia, court authorization is required before gonadectomy in a child can be performed.
- Disorders like 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency have the potential for significant virilization at the time of puberty and 50% or more will by then identify as male [12]. It is possible that in future some of the phenotypic variability that is seen will be found to relate to specific sequence changes in the affected gene and this information may be useful in predicting long term outcome [14].
- Partial androgen insensitivity. Male gender identity is much more common than was previously thought and fertility has occasionally been reported.

Age of presentation

In some parts of the world 46,XX children with non-salt losing CAH may present in mid-to late childhood so severely virilized (Prader 4 or 5) that their parents raised them as males. Their gender identity, by then, is often male and they reject any suggestion that they should live as females [15]. There is a spectrum of virilization and in less extreme cases, the girl may request clitoral reduction. The implications of this should be discussed with her and her consent, as well as that of the parents, is essential.

Among adolescents with DSD, there is a significantly higher prevalence of gender confusion and dysphoria than in the rest of the population. No assumptions should be made about their sexual orientation. They may appreciate being offered the services of a skilled and empathetic psychologist or counsellor at this stage of their lives.

Anatomical considerations

The sex of a newborn infant has always been decided on the basis of what their external genitalia look like and this is true in all cultures. When the genitalia are ambiguous, the approach to making this crucial decision may differ between rich and poor countries. In resource-poor countries, local traditions and culture initially dictate decision-making and usually, parents want the child to be male if this is considered possible. They may see severe under-virilization as a limiting factor in most situations. The relevant question is whether someone identifying as male in adult life would be happier with surgically-created female genitalia than with small male genitalia? Neither outcome is perfect. Parents in well-resourced settings may have similar concerns, but have ready access to the advice of medical specialists.

The anatomy of the internal genitalia also plays its part in the decision-making. In conditions like ovo-testicular DSD, the presence of a well-developed uterus would enhance the possibility of child bearing in the adult life with in-vitro fertilization, and hence help in decision making for rearing as a girl.

Potential for marriage and fertility

Infertility is highly probable in all forms of DSD other than in females with CAH. Even a small chance of fertility is better than none and allows room for hope. The removal of gonads also removes hope. Even a faint glimmer of hope for fertility may enhance a person's ability to marry and gain economic

independence from their parents in certain cultures. Because of this, they may be prepared to accept the risk of cancer.

Cultural and religious issues

It is vital to consider family background, education and the socio-economic situation when making long term management plans. Although less of an issue in developed countries, in many countries in Asia, Africa and the Middle east, male sex is the preferred option. Mostly, the cited reason is economic as it is presumed that men are more likely to be financially independent than women and for those on the Indian sub-continent, no dowry payment is attached to marriage for a man whereas it is for a woman. Sadly, the social acceptability of a unmarried man is far greater than for an unmarried women [16]. Both these facts are rapidly changing across cultures and its relevance for the ensuing 20–30 years should be considered while making these decisions in newborns. In Islamic cultures, a *fatwa* is a legal opinion provided by the religious law experts. In most Islamic countries fatwa allows sex change or similar surgeries in a DSD patient. An acceptance of these issues is improving with education status. In many countries, the legal ID card also has an option of a third gender identity.

Medical management

Hormone replacement

Congenital adrenal hyperplasia

Hormone replacement throughout life. A detailed discussion of the overall long-term medical management of CAH and the hormone replacement regime used is beyond the scope of this paper. We will assume that facilities and resources for good treatment and the monitoring of treatment are available and focus on the aspects of CAH that relate to it being a disorder of sex development. This, of course, only applies to girls with the condition. Optimal treatment is with hydrocortisone and fludrocortisone [17]. In the first few months of life, the kidneys are less responsive to mineralocorticoid than after this time, and oral salt supplementation is advisable. Blood pressure and linear growth should be monitored.

Girls with non-salt-losing CAH (and those with 11-beta hydroxylase deficiency) have a degree of clitoral enlargement and possible labial fusion at birth but are metabolically stable. If their life-long treatment with hydrocortisone starts from the time of diagnosis, the clitoris may shrink to some extent. If they are not treated, the clitoris will grow, linear growth will be accelerated, skeletal age will advance (leading to a reduction in final height) and virilization will be progressive. By the age of 9–10 years, the girl may start to identify as a boy. This highly undesirable outcome is completely preventable.

Later management issues that may arise

Early puberty. When CAH occurs in boys, delayed age of presentation may occur if salt loss is minimal or absent. These children present with rapid linear growth, signs of virilization without testicular enlargement and accompanying advance of bone age and elevated levels of 17 OHP and Testosterone supporting the diagnosis. Gonadotropins are suppressed unless the high androgen levels stimulate the hypothalamic pituitary axis, in which case central precocious puberty will occur as a secondary phenomenon. A similar presentation can be seen in girls who are non-salt losers, where early signs of virilization may not be reported by families and also in those children where very poor compliance with glucocorticoid medication over several years has resulted in inappropriate androgen secretion and early skeletal maturation. Loss of final height will be proportionate to degree of bone age advance and to ability to switch off puberty.

Various treatments have been used, including androgen blockade using spironolactone, anti-estrogen use with tamoxifen or flutamide (the latter with risk of hepatotoxicity) and addition of GnRH analogue in the presence of central activation.

Testicular adrenal rest tumor syndrome (TARTs). TARTs are benign tumors often present bilaterally within the rete testis. Documentation of presence of CYP B11 and CYP B12 receptors have supported the hypothesis that these represent an embryological presence of adrenal cells which, under stimulation of persistent or intermittent elevation of ACTH, undergoes hyperplasia into benign tumors, evident as testicular enlargement clinically and confirmed on ultrasound. Reported prevalence varying up to 50% in some series. Although they are prevalent where CAH control is sub optimal, they can also be seen in patients with good biochemical parameters. Complications can include infertility due to compression of gonadal tissue and sometimes to secondary hypogonadotrophic hypogonadism. Optimizing glucocorticoids may reverse early stages but advanced stages might require high dose dexamethasone and surgical removal.

Management problems in resource constrained environments. Availability of medications like hydrocortisone and fludrocortisone has been a major challenge in resource poor countries for a long time. In Pakistan and many other countries, despite being on the WHO essential medicine list there are no local manufacturers or importers for these medications, possibly because of low volume and profitability of the product. As a result, the only available sources are uncontrolled imports, both in terms of price and quality. Lack of a regular source of reliable local products also leads to periodic shortages, causing concerns for children and their families due to lack of alternatives. Organizations like Global Pediatric Endocrine and Diabetes (GPED), and Non Communicable Diseases (NCD child) are making global efforts for various legislations to ensure cost effective, sustainable availability of these life-saving medications [18].

Hormone replacement for other dsd conditions

Pubertal induction in boys

In conditions like mixed gonadal dysgenesis, PAIS and other DSD conditions when a decision has been made to rear as a boy, the majority will not be able to achieve pubertal progress with virilization and optimal linear growth without hormone replacement. Common practice is to administer small doses of testosterone (e.g. testosterone esters or testosterone enanthate) at a dose of 50 mg IM every month from around age 13 onwards. Every 6 months a small increment in dose is required till an adult dose of 250 mg once every 2–4 weeks is achieved, with maintenance replacement thereafter. In some countries long acting, flat profile testosterone injections, lasting 12–14 weeks may be used for maintenance of an adult hormonal milieu.

Pubertal induction in girls

Children with MGD and other DSD conditions who are being raised as girls, require estrogen replacement, to induce development of secondary sex characteristics, to achieve and maintain normal adult social, emotional and sexual health and for muscle and bone health. This may be required after gonadectomy for high risk of malignant gonadoblastoma or where gonadal function is absent or inadequate. Estradiol replacement is preferably commenced from the age of 11 years and gradually increased every few months to an adult dose of 2 μg per day of natural estrogen. A combined pill may then be used if more easily obtained. Alternatively, application of transdermal estradiol can be used, if available, by cutting down an estrogen patch to appropriate size, providing a dose of 0.05–0.07 μg/kg. Progesterone is only added when there is a uterus [19].

Surgical management

As the focus of this paper is on puberty, two scenarios which might bring a young person with a DSD to a surgeon (or gynaecologist) will be examined.

Scenario 1. A teenager with a previously undiagnosed DSD is referred

This could occur in the following situations:

- A girl found to have complete androgen insensitivity syndrome (primary amenorrhoea, absent pubic hair, inguinal masses thought to be testes, absent uterus, XY karyotype). The surgeon might be asked if the testes should be removed. The girl's vagina might be found to be very short and it might be asked what should be done to lengthen it. It is now considered preferable for the inguinal testes of girls with CAIS to be retained, as they secrete large amounts of testosterone after the onset of puberty and this is aromatized to oestrogen in the circulation, sufficient to bring about natural breast development and a female body shape, which is beneficial for boosting self-esteem. Androgen receptors are absent, so there is no risk of masculinization. There is a risk of testicular cancer after puberty and measures must be taken to monitor the testes closely if the young woman is not willing to give consent for their removal. Once they are removed, oestrogen replacement therapy is needed for life, but progesterone is not needed because there is no uterus. Women with CAIS are at risk of osteoporosis.
- A girl who has delayed puberty and complete gonadal dysgenesis with a Y chromosome. Imaging investigations would be needed to exclude an intra-abdominal gonadal malignancy. Laparoscopy would be needed to remove streak gonads to prevent cancer.
- A girl with non-salt losing CAH might have been kept at home and never been seen by a doctor. She would have marked virilization, a very large clitoris, hirsutism, possibly a deep voice and facial hair, and might well wish to be identified as a boy. The adrenals might be extremely large. If the surgeon is the first consultant to be involved, he or she would need to make referrals to other members of the multidisciplinary team for a precise diagnosis of the underlying condition and for medical treatment options. The girl's psychological state and social situation would need careful evaluation.
- A boy with impalpable testes could in fact have a 46,XX karyotype and be a fully masculinised female with undiagnosed non-salt losing CAH. He (an appropriate pronoun since he would identify as male) would most likely have a history of precocious puberty. Urethral bleeding, if it occurred, would be menstruation and this would need to be dealt with. Hysterectomy might be considered, but would remove all possibility of fertility that might be desired, even in this extremely unlikely situation. Surgery to make the genitalia female would probably not be considered as the patient would never consent to it. A conservative approach, with medical treatment to stop menstruation, would be in the patient's best interests.
- A boy with testes and a uterus might have insensitivity to anti-Mullerian hormone due to an AMH receptor mutation (persistent Mullerian duct syndrome). Anatomically, the spermatic ducts travel down the lateral walls of the uterus. Removing the uterus severs the spermatic ducts and renders the boy infertile, so it should not be done.
- A boy with an undescended testis and an abdominal mass. The mass could be a malignant seminoma if the underlying condition is 45,X/46,XY gonadal dysgenesis. The majority of patients with this karyotype have a male phenotype, rather than ambiguous genitalia.

Scenario 2. A teenager with a known DSD who has been managed since childhood by an endocrinologist is referred to a surgeon or gynaecologist

In this situation, the surgeon would be provided with details of the patient's past history and investigations and would be making an assessment of the patient's current needs. The patient might be:

- A girl with CAH who has had a clitoral reduction as an infant but no vaginoplasty. As she will soon begin menstruation, this surgery will need to be planned. Alternatively, the girl might not have had any surgery and she might want to discuss options relating to her large clitoris. It should not be assumed that every woman with an enlarged clitoris will want surgery to reduce its size as it does not necessarily prevent a happy sex life. The clitoris has only one function, which is to provide sexual pleasure. Surgery could damage the nerve supply and reduce sensation (although every attempt is made to spare the nerves on the dorsum of the clitoris) but this risk does not apply if the clitoris is left intact. Complete removal of the clitoris should be banned.

- A girl who has had a vaginoplasty as an infant and who is referred for a review. Sometimes shrinkage of scar tissue causes stenosis of the vaginal opening and dilatation may be necessary. It should be noted that young girls do not appreciate vaginal examination, especially by a male. The need for it should be carefully explained and the examination should not be done until the girl feels ready for it.

A girl known to have CAH but whose medical treatment has been sub-optimal. If psychological assessment shows that her gender identity is female, the girl would be informed about what surgery could offer (clitoral reduction) if she wanted it. In extreme cases, the child may be identifying as male and may ask for surgery to provide a phallus and penile urethra. If tissue has previously been removed, this may be virtually impossible. Feminizing genitoplasty for girls with CAH has been continued because labioplasty creates a separate vaginal opening, making it possible for them to have sex with a male when desired and hopefully become pregnant. The great majority of girls with CAH grow up with a female gender identity, provided hormone replacement has suppressed androgen secretion throughout childhood.

Acknowledging controversy

Whether surgery to alter the appearance of the external genitalia of an infant with DSD should or should not be offered has become a hotly contested subject and inevitably adolescent patients become aware of this through the internet. Their concerns should be acknowledged and respectfully addressed. Patient advocacy groups who are opposed to genital surgery on infants argue that having ambiguous genitalia is not a threat to health and therefore the surgery is not therapeutic. They also say that parents should not be able to consent to surgery that is not strictly needed for health reasons on behalf of an infant and that surgery is both invasive and irreversible, with major effects that carry the potential for undesirable outcomes, should adult sexual function be impaired or if the person develops a gender identity inconsistent with the genital sex that surgery has created for them. Threats of litigation have made surgeons in some countries extremely reluctant to remove gonads or to undertake clitoral reduction for lesser degrees of enlargement (Prader 3–4) and in Australia, such cases are now being referred to the Family Court.

Persistent concerns by adults who had been recipients of surgical interventions have prompted clinicians to examine outcomes. Work done by Creighton [20] indicated poor outcome results if surgery was done early, with many patients requiring redo-surgery. The 2005 Chicago Consensus Group recommended that surgery should only be considered for more severe degrees of virilization in girls [21]). It was proposed to delay intervention allowing a patient-determined gender orientation and sexual preference to guide surgical decision making and allow patient participation in consenting process.

However others have shown in multicenter studies that resolving early genital anatomy with sex assigned is promoted by patients as well as their parents [22]. Moreover further work by Creighton [21,23] minimal changes in practice with only slight reduction in vaginoplasties but no identifiable change in management of clitoromegaly. With this controversy still not resolved context, culture, religion and parental beliefs cannot be ignored as they are often the decision makers.

The aims of surgery, when this route has been decided on, are to restore functional genital anatomy allowing penetrative intercourse, facilitate future reproduction when possible, avoid UTI and fluid retention in the vagina and to avoid late virilization in girls or breast development in boys [24]. The surgery should reduce risk of future cancer and allow development of social identities [18].

Surgical outcomes

The surgical outcomes after feminizing genitoplasty are generally reported good in hands of pediatric surgeons with specific expertise in DSD surgery [25] with a complication rate of 7.6% Postoperative infections and urinary incontinence are rare but can be seen in total urethral mobilization (TUM) [26]). Vaginal stenosis is a possible complication of vaginal reconstruction requiring evaluation as child grows and correction if significant. Clitoral pain or decreased sensation can be associated with

clitorectomy. Surgical techniques can have an impact on outcomes in sexual satisfaction and gender identity [27]) Long-term follow up and patient reported feedback is crucial.

Surgery in context

Family dynamics and cultural context should be important drivers of decision and sex of rearing. Authors have been faced with dilemmas where late presenting 46,XX CAH girls have been raised as boys and family dynamics do not permit gender reassignment. In such a scenario 2 staged Bracka Hypospadias repair along with complete hystero-salphango-opherectomy has been performed [28].

Timing of surgery in CAH

Much debate has been generated about the timing of surgery and if it should be done at all. Suggestions that feminizing genitoplasty may cause adverse effects on sexual life of the patients in adulthood like loss of sexual sensitivity or dyspareunia have led to some suggestions to avoid surgery altogether [29]. This led patient advocacy groups and human rights organizations to raise issues of informed consent and to assert that only the patient herself should be able to give consent. Some human rights groups have considered surgery as a form of mutilation and child abuse. This remains a controversy, with strong opinions on both sides of the divide, especially in the western world. However, the situation is different in many parts of the world.

Particular considerations in different cultural settings

In a conservative, Islamic society with strong patriarchal influences, parents are keen for surgery as soon as a diagnosis of DSD is made. They remain secretive, hiding the diagnosis even from immediate family. Many parents do not want disclosure that their daughter has even visited a specialist let alone undergone surgery. External female appearance is paramount in their view. Similarly, gender issues are often layered in secrecy, such that older children, heavily virilized and raised as boys are frequently seen. A multidisciplinary approach helps to counsel these patients and families. A clear decision to raise the child as a girl or a boy as soon as possible after diagnosis is very helpful, as that choice, once taken, often difficult to change. Unfortunately for many children and their families access to experts dealing with such issues is not available.

Quality of life/mental health

Management of children with DSD poses many challenges in terms of mental health and psychosocial issues. Incongruence between physical appearance and assigned sex may impair psycho-social adaptation and create profound psychological distress, further influenced by different educational, social economic, religious backgrounds of families and ability to address the problems, along with limitation of access to expertise in health sectors across the globe. A recent international survey has indicated the presence of such expertise in only 41% of centers [30], Systematic psychosocial screening has been recommended in all case management of children with DSD [31].

Practice points

- Detailed history to include family history of consanguinity, infant deaths or similar conditions
- Multidisciplinary team is needed to provide optimal care of an infant or child with a DSD
- Meticulous counselling should be undertaken, to avoid family confusion
- Congenital adrenal hyperplasia is a life threatening condition, mandating early diagnosis
- Mixed gonadal dysgenesis is likely where there is genital asymmetry with one palpable gonad

Research agenda

- Multiple parallel or whole genome sequencing to help better define DSDs
- Methods for better education of medical, allied health staff and families for early identification of DSD
- Defining an optimal age for and extent of genital reconstructive surgery

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.beem.2019.101297.

References

*[1] Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. J Pediatr 2006;118(2):e488–500.
[2] González R, Ludwikowski B. Should CAH in females be classified as DSD? J Front Pediatr 2016;4:48.
*[3] Ahmed SF, Achermann JC, Arlt W, et al. Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015). J Clin Endocrinol 2016;84(5):771–88.
[4] Brain CE, Creighton SM, Mushtaq I, et al. Holistic management of DSD. J Best Prac Res Clin Endocrinol Metabol 2010;24(2):335–54.
[5] Khan SI, Hussain M, Parveen S, et al. Living on the extreme margin: social exclusion of the transgender population (hijra) in Bangladesh. J Health Popul Nutr 2009;27(4):441.
[6] Mondal R, Ray S, Chatterjee K, et al. Penile length and testicular volume in newborns. Indian J Pediatr 2016;83(12–13):1398–404.
*[7] Ahmed SF, Khwaja O, Hughes IA. The role of a clinical score in the assessment of ambiguous genitalia. BJU Int 2000 Jan;85(1):120–4.
[8] Croft B, Ayers K, Sinclair A, et al. Review disorders of sex development: the evolving role of genomics in diagnosis and gene discovery. Birth Defects Res C Embryo Today 2016 Dec;108(4):337–50.
[9] Tannour-Louet M, Han S, Corbett ST, et al. Identification of de novo copy number variants associated with human disorders of sexual development. PLoS One 2010;5(10):e15392.
[10] Ledig S, Hiort O, Scherer G, et al. Array-CGH analysis in patients with syndromic and non-syndromic XY gonadal dysgenesis: evaluation of array CGH as diagnostic tool and search for new candidate loci. J Human Reprod 2010;25(10):2637–46.
*[11] Eggers S, Sadedin S, Van Den Bergen JA, et al. Disorders of sex development: insights from targeted gene sequencing of a large international patient cohort. J Genome Biol 2016;17(1):243.
[12] Mieszczak J, Houk CP, Lee PA. Assignment of the sex of rearing in the neonate with a disorder of sex development. Curr Opin Pediatr 2009 Aug;21(4):541–7.
*[13] Kreukels BP, Köhler B, Nordenström A, et al. Gender dysphoria and gender change in disorders of sex development/intersex conditions: results from the dsd-LIFE Study. J Sex Med 2018;15(5):777–85.
[14] Avendaño A, Paradisi I, Cammarata-Scalisi F, et al. 5-α-Reductase type 2 deficiency: is there a genotype-phenotype correlation? A review. Hormones (Athens) 2018 Jun;17(2):197–204.
[15] Jorge JC, Echeverri C, Medina Y, et al. Male gender identity in an XX individual with congenital adrenal hyperplasia: a response by the authors'. J Sex Med 2009;6(1):298–9. Hormones (Athens). 2018 Jun;17(2):197-204.
*[16] Joseph AA, Kulshreshtha B, Shabir I, et al. Gender issues and related social stigma affecting patients with a disorder of sex development in India. Arch Sex Behav 2017;46(2):361–7.
*[17] Speiser PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2018;103(11):4043–88.
[18] Zacharin M, Chanoine JP, Cassorla F, et al. l 70 global pediatric endocrinology and diabetes active members promoting excellence in the care of pediatric endocrine diseases in the developing world. Pediatrics 2013 Feb;131(2):e573–8.
[19] Ankarberg-Lindgren C, Kriström B, Norjavaara E. Physiological estrogen replacement therapy for puberty induction in girls: a clinical observational study. Horm Res Paediatr 2014;81(4):239–44.
[20] Creighton SM, Minto CL, Steele SJJTL. Objective cosmetic and anatomical outcomes at adolescence of feminising surgery for ambiguous genitalia done in childhood. Lancet 2001;358(9276):124–5.
[21] Creighton SM, Michala L, Mushtaq I, et al. Childhood surgery for ambiguous genitalia: glimpses of practice changes or more of the same? Psychol Sex 2014;5(1):34–43.
[22] Binet A, Lardy H, Geslin D, et al. Should we question early feminizing genitoplasty for patients with congenital adrenal hyperplasia and XX karyotype? J Pediatr Surg 2016;51(3):465–8.
*[23] Michala L, Liao L-M, Wood D, et al. Practice changes in childhood surgery for ambiguous genitalia? J Pediatr Urol 2014;10(5):934–9.
*[24] Vidal I, Gorduza DB, Haraux E, et al. Surgical options in disorders of sex development (dsd) with ambiguous genitalia. Best Pract Res Clin Endocrinol Metabol 2010;24(2):311–24.

[25] Lean WL, Deshpande A, Hutson J. Grover SR Cosmetic and anatomic outcomes after feminizing surgery for ambiguous genitalia. J Pediatr Surg 2005 Dec;40(12):1856–60.
[26] Dangle PP, Lee A, Chaudhry R, et al. Surgical complications following early genitourinary reconstructive surgery for congenital adrenal hyperplasia-interim analysis at 6 years. Urology 2017 Mar;101:111–5.
[27] Wang LC, Poppas DP. Surgical outcomes and complications of reconstructive surgery in the female congenital adrenal hyperplasia patient: what every endocrinologist should know. J Steroid Biochem Mol Biol 2017 Jan;165(Pt A):137–44.
[28] Bracka A. Hypospadias repair: the two-stage alternative. Br J Urol 1995 Dec;76(Suppl. 3):31–41. 30.
*[29] Mouriquand PD, Gorduza DB, Gay C-L, et al. Surgery in disorders of sex development (DSD) with a gender issue: if (why), when, and how? J Pediatr Urol 2016;12(3):139–49.
[30] Kyriakou A, Dessens A, Bryce J, et al. Current models of care for disorders of sex development—results from an international survey of specialist centres. Orphanet J Rare Dis 2016;11(1):155.
[31] Sandberg DE, Gardner M, Callens N Mazur T. DSD-TRN psychosocial workgroup, the DSD-TRN advocacy advisory network, and Accord Alliance Interdisciplinary care in disorders/differences of sex development (DSD): the psychosocial component of the DSD-Translational research network. Am J Med Genet C Semin Med Genet 2017 Jun;175(2):279–92.