

# Disorders of sex development (DSDs), their presentation and management in different cultures

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**Abstract** The way disorders of sex development (DSD) are viewed and managed in different cultures varies widely. They are complex conditions and even well-educated lay people find them difficult to understand, but when families are very poor and lacking in basic education, and the health system is starved of resources, traditional beliefs, folk remedies and prejudice combine to make the lives of children and adults with DSD extremely difficult and sad. Rumour and discrimination isolate them from their communities and they become devalued. People with DSDs desire the same things in life as everyone else—to find someone who will love them, to be valued as human beings, to feel at home in their own bodies, to be able to have satisfactory sexual relations should these be desired, to be able to trust their medical advisers and to be integrated into the general community. Long term outcome studies have been published from many countries, but these studies have not necessarily been critical of the values that underpinned the type of treatment given to the patients. There is a need for standardized instruments that would allow a true comparison of the quality of outcomes *from the patients' perspective*. Much could be done to improve

equity between rich and poor countries for the benefit of people with DSDs. A focus on developing cheap, robust diagnostic tests, making essential medicines available for all, training surgeons to do better operations, educating health professionals, families and the general community in order to break down prejudice against people with DSDs, and training mental health workers in this specialized field, would do much to alleviate the burden of the condition.

**Keywords** Disorders of sex development · Culture · Long-term outcome · Genital surgery · Gender identity · Poverty

## 1 Introduction

Disorders of sex development (DSDs) occur with an incidence of 1:4,500 to 1:5,000 live births [1, 2]. A DSD is defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical. DSDs can be subdivided into three main groups: disorders associated with gonadal dysgenesis; disorders associated with undervirilization of 46,XY individuals; and conditions associated with prenatal, and possibly also postnatal, virilization of 46,XX subjects. Some DSDs are associated with obvious genital ambiguity at birth, while in others the external genitalia are typically male or typically female, but the internal anatomy is discordant.

DSDs are always challenging to manage. Choosing the optimal gender is difficult when the genitalia are ambiguous. Genital surgery is often required and both the type and the timing of surgery raise controversial issues. Underlying endocrine disturbances are present in most cases and usually require long term medication. Fertility is impaired in nearly

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all DSDs. Gonadal development is impaired in the first two of the above three categories and in most cases is associated with increased risk of neoplasia. There is the risk that childhood and adolescence for affected individuals will be compromised by gender dysphoria and other psychosexual difficulties, which may carry over into adult life.

Recently published consensus guidelines [3] advocate early and accurate diagnosis, a holistic team-oriented approach to management, with professional mental health support for patients and families, a patient-centered and evidence-based process for decision-making, expertly performed surgery carried out by a pediatric surgeon (preferably a urologist) in a centre of excellence, optimal hormonal management and close tracking of patients and families over a long period. In relation to one specific condition, congenital adrenal hyperplasia, consensus guidelines from an international workshop held at Gloucester, Massachusetts in 2002 [4] recommended newborn screening, hydrocortisone as the optimal glucocorticoid, fludrocortisone for all cases of salt-wasting CAH, early diagnosis utilizing a 17-hydroxyprogesterone assay, and surgery performed in infancy or early childhood for girls with ambiguous genitalia. Prenatal diagnosis and treatment were also endorsed.

## 2 Clinical presentations of DSD

DSDs may cause changes that are immediately visible in the newborn infant, or they may cause changes that are only detected and presented to the doctor when the child is older or has even reached adolescence. The range of presentations can be summarized as follows:

1. Ambiguous genitalia: generally recognized when the baby is newborn or soon afterwards
2. Manifestations of DSD that are not recognized until later in childhood or in adolescence:
  - (a) The girl found to have either testes or dysgenetic gonads and who proves to be Y-chromosome positive.
  - (b) The adolescent girl with primary amenorrhoea who is found to have no uterus and/or vagina. She may be 46,XX and have ovaries or be 46,XY and have testes or streak gonads.
  - (c) The boy with impalpable or inguinal testes who is found at surgery to have a uterus and Fallopian tubes and who is 46,XY (e.g. ovotesticular DSD; persistent Mullerian Duct Syndrome)
  - (d) The boy with impalpable gonads who is found to have ovaries and a uterus. Occasionally the first abnormality to be recognized is penile bleeding, which is in fact menstruation.

- (e) The girl who, although born with typical female genitalia, undergoes progressive clitoral enlargement and other signs of virilization during childhood.

## 3 Classification

DSDs are classified according to the chromosomes, the gonadal histology and the phenotype. The classification that is currently advocated is summarized in Table 1.

Table 2 shows the correlation between the mode of clinical presentation and the most likely underlying cause.

Supported by good facilities for investigation, clinicians can follow an algorithm that in many cases will lead to an aetiological diagnosis [5]. The availability of paediatric endocrinologists is a key factor in determining whether or not the cause of a DSD can be investigated. Endocrinologists in well resourced countries would expect to have most of the following facilities available to them:

1. Cytogenetics
2. Biochemistry
  - (a) Assays for serum 17-hydroxyprogesterone, testosterone, estradiol, DHT, androstenedione, DHEAS, FSH, LH (and if possible, MIS and inhibin B)
  - (b) Urine steroid analysis by GC–MS
3. Imaging—ultrasound, MRI
4. Endoscopy
5. Histopathology and immunohistochemistry
6. Molecular genetics—AR, SRY, SF1, WT1, CYP21, DAX-1, 17 $\beta$ HSD, 5 $\alpha$ Reductase-2, and others

Paediatric endocrinology is still a developing specialty in resource-poor areas and even large populations such as in India, Pakistan, China, Indonesia and Vietnam have very few paediatric endocrinologists. The small number of reports on DSD case series from developing countries suggests that diagnostic facilities are extremely limited in both distribution and quality. Cytogenetic services may be available, but the standard of testing may not be adequate for the detection of chromosomal mosaicism. Steroid assays beyond those that have application in adults (testosterone, oestradiol, progesterone) are rarely available and even 17-hydroxyprogesterone assays are unavailable in many parts of the developing world. MRI is not usually available. There are few experts in paediatric histopathology. Molecular genetic analyses cannot be done. With this lack of diagnostic tools, clinicians have to work under severe constraints and it is very difficult to make an accurate diagnosis. Many diagnoses have to be made by informed guesswork. Patients who are 46,XX are assumed to have congenital adrenal hyperplasia, and those who are 46,XY are usually left without a more detailed diagnosis.

**Table 1** A classification of DSDs

Sex chromosome DSD	46,XY DSD	46,XX DSD
45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)	Disorders of gonadal (testicular) development Complete gonadal dysgenesis (Swyer syndrome)  Partial gonadal dysgenesis Gonadal regression Ovotesticular DSD	Disorders of gonadal (ovarian) development Ovotesticular DSD Testicular DSD (e.g. SRY + , dup SOX9) Gonadal dysgenesis
46,XX/46,XY (chimeric, ovotesticular DSD)	Disorders in androgen synthesis or action Androgen biosynthesis defect (e.g. 17 hydroxysteroid dehydrogenase deficiency, 5 $\alpha$ reductase deficiency, lipoid adrenal hyperplasia (StAR mutations) Defect in androgen action (e.g. CAIS, PAIS)  LH receptor defects (e.g. Leydig cell hypoplasia, aplasia) Disorders of AMH and AMH receptor (persistent Mullerian duct syndrome)	Androgen excess Foetal (e.g. 21 $\alpha$ -hydroxylase deficiency, 11 $\beta$ -hydroxylase deficiency)  Foetoplacental (aromatase deficiency, oxidoreductase deficiency) Maternal (luteoma, exogenous, etc)
Other	e.g. severe hypospadias, cloacal extrophy	e.g. cloacal extrophy, vaginal atresia, other syndromes

(Adapted from reference 3)

**4 A proposed framework for decision making, based on ethical principles**

Medical decision-making in relation to patients with DSDs is complicated and often very difficult. There are some important universally applicable ethical principles (Associate Professor L.H. Gillam, Clinical Ethicist, the Royal Children’s

Hospital Melbourne, personal communication). that can be used. The needs are:

1. Minimizing physical risk to child, e.g.
  - (a) Malignancy (the risk of gonadal cancer is increased in XY gonadal dysgenesis, PAIS, etc)

**Table 2** Correlation between mode of clinical presentation and underlying cause

Mode of presentation	Commonest causes
Ambiguous genitalia	46,XX DSD due to congenital adrenal hyperplasia (21-hydroxylase deficiency) Sex chromosome DSD (e.g. 45,X/46,XY partial gonadal dysgenesis and ovotesticular DSD) 46,XY Partial androgen insensitivity syndrome 46,XY 5 $\alpha$ -Reductase-2 deficiency 17 $\beta$ -hydroxysteroid dehydrogenase deficiency
The Y(+) girl found to have either testes or dysgenetic gonads	46,XY DSD due to Complete androgen insensitivity syndrome (CAIS) 46,XY DSD due to complete gonadal dysgenesis
The adolescent girl with primary amenorrhoea who is found to have no uterus and/or vagina. She may be 46,XX and have ovaries or be 46,XY and have testes	46,XX Müllerian agenesis 46,XY CAIS
The 46,XY boy with impalpable or inguinal testes who is found at surgery to have a uterus and fallopian tubes	46,XY persistent Müllerian duct syndrome
The boy with impalpable gonads who is found to have ovaries and a uterus. Or the older boy with impalpable gonads who presents with isosexual precocious puberty	46,XX DSD due to congenital adrenal hyperplasia (21-hydroxylase deficiency)
The girl who, although born with typical female genitalia, undergoes progressive clitoral enlargement and other signs of virilization during childhood or adolescence	46,XY DSD due to 17 $\beta$ -hydroxysteroid dehydrogenase deficiency

- (b) Osteoporosis (risk is increased if gonads have been removed without hormone replacement therapy)
  - (c) Adrenal crisis (increased risk in CAH)
  - (d) Urinary passage obstruction (as in girls with fused labia and a urine-storing vagina)
2. Minimizing psycho-social risk to child, e.g.
    - (a) Risk of assigning wrong gender, leading to later gender dysphoria
    - (b) Risk that child will be unacceptable to parents, leading to impaired bonding.
    - (c) Risk of social/cultural disadvantage to child
    - (d) Risk of social isolation, embarrassment, distress etc e.g. having genitalia which do not match social sex
  3. Preserving potential for fertility
    - (a) Having gonadal structures
    - (b) Having viable gametes
    - (c) Being able to carry pregnancy
  4. Preserving or promoting capacity to have satisfying sexual relations
  5. Leaving options open for the future (e.g. not removing gonadal or phallic tissue unless necessary to do so)

## 5 Conditions in developing countries

### 5.1 Education

The resource-poor environment of a developing country is not very conducive to the implementation of guidelines such as those listed in the two LWPEs–ESPE consensus statements. Per capita income and standards of living are low, there are low levels of education and life expectancy, technical facilities in hospitals and laboratories are under-resourced, supply of essential medicines cannot be guaranteed and communication systems are weak. One of the major constraints is that the logistic difficulty experienced by people wishing to access the traditional or allopathic health care system is so great that they are compelled to use alternative medicine. Doctors and other healthcare workers serving in resource-poor environments have far less access to continuing medical education than their counterparts in developed countries and outside major centers, may only be familiar with very common conditions.

### 5.2 Health economics

The health budgets of developing countries are almost entirely consumed by public health priorities, such as immunization and the provision of clean water and the treatment of acute medical conditions, such as those related to malnutrition, infectious disease and accidents. Misuse of

resources is also common, with priorities being given to the purchase of expensive equipment and tertiary care. Policies that provide for the management of chronic medical conditions are often lacking, so that patients requiring on-going medicine supplies either have to pay for them without any government support, or do without. Health care is not government supported and health insurance provides cover for very few people. Hospitals and other medical facilities are often over-crowded and expensive and community-based medical care is likely to be very basic. Very little privacy is possible when several doctors are working with different patients in the same noisy room and there is no separate, screened area for physical examination. Rural families, who make up most of the population, are likely to avoid hospitals until they have exhausted all hope that cheap, locally available traditional herbal remedies and alternative treatments will suffice.

### 5.3 Traditional values and beliefs

Traditional values and beliefs are often strong in various cultures. They can play a very crucial role especially in situations like DSD, which is difficult to explain scientifically and poorly understood by the common man, and are fertile ground for the generation of myths misconceptions that are purported to explain such problems. This is often compounded by the fact that sexual issues are taboo subjects in certain societies and parents do not want to discuss them even with the medical professionals. Resorting to faith healers, shrines and purveyors of magic is more natural for them.

### 5.4 Family survival, preference for sons, and the marriage imperative

In developing countries, birth rates and also infant mortality tend to be high. The high mortality leads to insecurity, driving the birth rate and family size higher, and placing increased pressure on the breadwinner's capacity to provide food for the family. The lack of social security provisions such as pensions in developing countries means that when they are no longer able to do productive work, parents are totally dependent on their children for survival. Children are a form of insurance against a miserable old age. In many cultures, the eldest son has special responsibilities for both the physical and the spiritual welfare of the parents, and this is one powerful reason why sons may be valued more highly than daughters. The child on whom the parents depend for survival needs to be economically independent, and this means being married and being employed. (Interestingly, when the eldest daughter is the bread winner, parents may not want her to get married for the fear of their own well being). Infertility, especially for a woman, may

make it difficult, even impossible, for her to marry and being unmarried may carry such a stigma that she may not get a job, with the result that she will become a burden for the family and a social outcast. Instead of being able to take care of her elderly parents, she will be seen as liability.

All of these factors operate when a baby born in a resource-poor environment is found to have a DSD. The parents may prevaricate about seeking medical attention in the first instance and undoubtedly, some infants die due to neglect. It has also been shown in a number of studies that medical care is sought more for boys than in girls: our own data from the National Institute of Child Health in Karachi, Pakistan showed, in contrast to the western literature, that more boys than girls were brought for medical assessment of ambiguous genitalia [6]. We also found that the majority of CAH patients who presented had the non-salt wasting variant, whereas in other countries, newborn screening always shows that salt wasting CAH comprises 75% of babies diagnosed. The inescapable conclusion is that in Pakistan, many babies with salt wasting CAH die undiagnosed. Those who survive often present late, exacerbating any progressive physical and psychological changes caused by the underlying hormonal condition. Two papers [7, 8] have examined long term outcome for DSD patients from India and Vietnam. Poverty seems to be the main factor affecting long term outcome as it denies the patient access to early diagnosis (lack of clear referral pathways, inadequacy of laboratory services), accurate medical advice (lack of experienced specialists), appropriate medicines, high quality genital surgery (lack of international benchmarking, lack of paediatric surgeons and lack of adolescent gynaecology services) and mental health services.

### 5.5 Consanguinity

Consanguinity is very common in India, particularly among Hindus of south India and among Muslims all over India. Conditions such as congenital adrenal hyperplasia, which are perpetuated by autosomal recessive inheritance, are likely to affect multiple family members and to occur with greater frequency than elsewhere. A good example is the high prevalence of 21-hydroxylase deficiency among the Yupik Inuit of Alaska.

### 5.6 Rumour and discrimination

It is extremely common for parents of children with DSDs to experience guilt, anxiety and depression after the diagnosis has been made and their natural reaction is to keep the child's condition a closely-guarded secret, even from close relatives [9]. This serves to further isolate them and aggravate their distress. The parents' fear is that if the child's condition becomes widely known, both they and the child will suffer

from being the subject of rumour and discrimination. Our observation is that this kind of discrimination is real and that it occurs in village communities as well as in sophisticated city environments. In the Indian sub-continent, the existence of a large sub-culture known as *hijra* (also referred to as 'hermaphrodites', 'eunuchs' and 'ostracized society') has a particularly potent influence on the thinking of parents when a child with ambiguous genitalia is born. In popular belief, hijra are people who were born with an intersex condition and who choose to live apart in separate communities that maintain their numbers by kidnapping babies with ambiguous genitalia. They are greatly feared and reviled. The mere suggestion that a baby born with ambiguous genitalia may be a hijra is enough to cause tremendous fear in the parents. Hijra mostly look like males, but dress themselves as females with heavy makeup. They live as a group, often at shrines or safe locales, and earn their living by begging on streets and/or singing and dancing at weddings. They are commonly perceived as 'hermaphrodites', but the little work that has been done on them has shown them to be a mixed bag of individuals. Some of them are homosexual or transsexual individuals who join the group because their lifestyle is otherwise prohibited in the society. Some are boys who have been kidnapped and castrated [10]. Others may be normal men posing as hijras to earn a living, some of them may be actually street criminals or drug addicts who join the ranks, and some may actually be ambiguous genitalia patients, again not properly investigated or treated but mostly abducted or given to them by the parents. They are generally operating in the form of a ring with a ring leader and often don't like anyone probing into their activities.

In Vietnam, we learned that an extremely derogatory colloquial phrase, *ai nam ai nu*, which literally means "neither male nor female", is used without distinction in reference both to people born with genital anomalies and to homosexuals, so that all are tarred with the same brush. Health professionals sometimes use the term when advising parents, showing that their own attitudes could do with some improvement.

## 6 Management issues affected by culture and economics

### 6.1 Selecting the optimal gender

Over the past 20 years in the west there has been a shift away from an earlier policy that recommended female sex of rearing for most 46,XY infants born with ambiguous genitalia. That policy was based on the thesis, now challenged, that gender identity had everything to do with nurture and nothing to do with nature. In other words, it was believed that prenatal exposure to androgen did not

affect the developing brain in humans and that making the genital appearance female by surgical intervention, combined with reinforcement of the female gender by the parents, would result in the development of a stable female gender identity. An additional reason for selecting female gender more than male was that the surgery to make male genitalia was more difficult to perform and would often result in a very small penis. It does appear true that the main determinant of adult gender identity is the initial gender assignment [9] but unfortunately some XY patients raised female develop gender dysphoria and in some cases, a profound gender identity disorder leading them to request gender reassignment and further surgery to reverse the original operation. We advocate male sex of rearing for most children with the combination of ambiguous genitalia and XY chromosomes, provided that a strategy to manage the increased risk of gonadal malignancy has been set in place. This option preserves choice better than the option of feminizing genitoplasty, which involves removal of genital tissues. An exception might be made in cases of ovotesticular DSD (most of whom are, in any case, 46XX) who have a uterus, because the ovarian component of the gonads may contain viable oocytes; the testes however are usually much more dysplastic and spermatogenesis is absent.

Reports from other cultures, such as India [11–13], Turkey [14], Saudi Arabia [15], Malaysia [16] and Thailand [17] indicate a strong tradition for Asian and Middle Eastern parents to select male gender for their children born with ambiguous genitalia. In a country like India or Pakistan, DSD patients raised male, even if they are infertile, are more likely to achieve economic independence than patients raised female who are infertile. An infertile female will not be offered in marriage in a culture that encourages arranged marriages. Marriage confers respectability on a woman, and to remain unmarried is shameful for the woman and her parents; she will be dependent on them for support because no-one will employ her. On the other hand, a man has many advantages: he can inherit his father's wealth whereas a daughter may have no entitlement or only be entitled to inherit a half share, depending on the context and community. A Muslim male can worship with the men in the mosque. He can become a priest or other kind of religious leader. Employment opportunities will be open to him. In Hindu society, the eldest son has the ceremonial duty to light his parents' funeral pyre.

In the west, when selection of the optimal gender is being considered, a great deal of attention will be paid to whether or not the child will grow up able to enjoy sexual pleasure and fulfillment. Many long term outcome studies [18, 19] have focused on this. Eastern thinking, in contrast, is more concerned with ensuring that the individual (especially if brought up as a girl) will be capable of having sexual intercourse to satisfy the partner.

## 6.2 Genetic diagnosis and counseling

Most DSDs have a genetic basis and genetic counseling forms part of patient care. The concepts of genetics are poorly understood by most people living in communities with low levels of general education. Diseases may be understood in terms quite foreign to the doctor trained in modern medicine. In India, for example, a birth defect may be attributed to the parents having broken some social taboo during the pregnancy, or even be related retrospectively to inadequacy of the baby massage provided when the baby was born. In southern Africa, a DSD is thought to be the result of witchcraft. Genetics, while taught, may not be a major part of the undergraduate curriculum in medical schools and many paediatricians know very little about the subject, especially in the absence of adequate numbers of specialists able to help others understand the complex issues. There are no professional genetic counselors. Lack of genetic understanding of the disorder promotes the influence of faith healers, myths, and taboos. Women, being the inferior gender, often bear the blame for these defects. Marital life is often affected by this. In extreme cases, the husband may even demand annulment of the marriage. The parents of children with DSD may not receive any genetic counseling at all, even by the doctor. They may therefore have more than one child with the same condition, which is a disaster if the family was already poor. The chances of a second affected child surviving under these circumstances would be slim.

Prenatal testing and prenatal diagnosis for congenital adrenal hyperplasia are not yet available in most developing countries. Whereas in the west, prenatal diagnosis would usually be done in the context of prenatal treatment of the mother with dexamethasone to prevent genital ambiguity in an affected female foetus, in a developing country it is more likely that parents would decide to terminate the pregnancy if they knew the foetus was affected. Newborn screening for CAH has been established on a local scale in some developing countries, including the Philippines and Vietnam.

## 6.3 Surgical interventions

Around the world there is no standard, universally accepted operation for feminizing genitoplasty and there are many to choose from [20]. In some procedures, the entire shaft of the clitoris is excised, leaving only the glans and its neurovascular bundle. In others, the ventral half of the shaft is removed, leaving the dorsal half and the glans. Comparative studies have not been done. Some quality of life studies [19, 21] indicate a high level of impairment for women with DSDs especially for those with CAH (the largest group in most studies). The quality of surgery in developing countries is highly variable because there are

very few paediatric surgeons who have been trained in the modern techniques of genitoplasty, therefore many operations on infants and children are performed by general surgeons who have had little training to prepare them for this kind of surgery. Removal of the entire clitoris is still practiced in developing countries. Hypospadias surgery is always difficult and even in good centres, some patients need multiple operations. The level of difficulty is compounded by the development of serious complications, such as urinary fistula. Fear of surgery leads many families to avoid it for as long as possible, and this leads patients to present with advanced features of virilization by which time the clitoris may be very large and the child may be experiencing gender dysphoria. There is very little privacy for children when growing up in a joint family; a girl child may have to take a bath in the presence of her female cousins and aunts and likewise for a boy. In such an environment, there is little chance for the policy of late removal of organs discordant to the sex of rearing to succeed. There is no long term follow up except in the largest centers, so results about quality of life are unknown.

#### 6.4 Managing the risk of cancer

Intra-abdominal testes, especially if they are dysgenetic, are associated with a markedly increased risk of germ cell cancer [3]. Dysgenetic testes that are in the scrotum also carry an increased risk, probably of a lower order. Good patient care requires a strategy to manage this risk and protect the patient from an early death. Knowing about the risk is the first step. Telling the parents, and later the patient, about it is the next. Eliminating the risk might involve removing both gonads if pre-malignant or frankly malignant histological changes are detected in a biopsy. Not all pathologists have the specialized training needed to recognize carcinoma-in-situ, which makes it very difficult for doctors in developing countries to implement modern, testis-sparing conservative risk management strategies. Uneducated parents may strongly resist advice that would lead to the removal of testes if they cannot understand concepts of probability and if they are unable to accept that there was no chance of fertility anyway. The removal of gonads also means that life-long hormone replacement therapy will be needed, and this may be beyond what the family's budget can stand. In developing countries, patients present later than they would in other countries, and they are therefore more likely to have cancer already when they first present.

#### 6.5 DSDs that occur more commonly in developing countries

In certain areas of the world, there are areas of high incidence for certain genetic forms of DSD. 5 $\alpha$ -Reductase

deficiency was first reported on one island in the Dominican Republic [22]. It is also prevalent in southern Lebanon [23], the Eastern Highlands Province of Papua-New Guinea [24] but is relatively rare in the Caucasian race. Steroid

17 $\beta$ -Hydroxysteroid dehydrogenase deficiency is very common in the Gaza Strip [25]. Both of these conditions can lead to a gradual transition in gender identity from female to male. In southern African blacks, 46,XX ovotesticular DSD has an unusually high prevalence [26].

#### 6.6 Availability of medicines

Developing countries rely on international advice from organizations such as the World Health Organization in setting priorities for their Essential Medicines List [27]. The Essential Medicines List is a model list of medicines that WHO considers should be freely available to populations. While countries are free to modify it and produce their own lists, many adopt it in its original unmodified form and use it as the basis for what they will license for import; they also take the list into account when deciding whether or not to impose taxes. The 2007 edition lists only one oral steroid—prednisolone (5 and 25 mg tablets)—as well as injectable forms of hydrocortisone and dexamethasone. Hydrocortisone is not listed, and neither is fludrocortisone. There is evidence to show that in growing children, hydrocortisone (which is short-acting) is superior to the longer-acting prednisolone, which impairs linear growth to a much greater extent [28]. The reason for the non-inclusion of these important medicines is simply that no application for their inclusion has been made! The unavailability of oral hydrocortisone and fludrocortisone in developing countries impacts heavily on children with salt wasting congenital adrenal hyperplasia. These medicines must either be bought at exorbitant prices on the black market [29] or done without. Doing without fludrocortisone often means certain death for a child with salt wasting variety of congenital adrenal hyperplasia. Even if a drug is on the Essential Medicines List, cost will still be a limiting factor because few, if any, developing countries are able to provide any subsidy to help poor families buy medicines. Even inexpensive medications such as oestrogen and testosterone may be priced out of the reach of poor families, which means that children and adults with hypogonadism for any reason may not have access to the life-long hormone replacement that they need. Therefore, if essential medicines are to be made available to everyone who needs them, rich or poor, the drug needs to be on the Essential Medicines List, and attention needs to be given to the alleviation of poverty so that poor families can get the drugs they need. Ideally this would be in the form of a government subsidy, but in the absence of that, a strategy to

help poor families earn more money would be an alternative option to consider.

An Australian charity, CLAN (Caring and Living as Neighbours [30]) has developed a strategic approach that it hopes will improve outcomes for children with CAH (and other chronic diseases) living in developing countries. The strategy depends on five pillars:

1. Optimise affordability and availability of medications (initially by donating essential medicines, then by advocacy directed at the pharmaceutical industry and government to achieve registration)
2. Education (of patients, families, health care workers, government bodies, policy makers and the international community)
3. Optimise medical treatment
4. Encourage family support groups
5. Assist in reducing the financial burden of chronic medical conditions in childhood that lead to poverty e.g. by involving microfinance institutions, as well as by trying to influence government policies around insurance.

Implementation of the CLAN strategy has begun in Vietnam, the Philippines, Indonesia and Pakistan.

### 6.7 Management of patients who present late

Endocrine clinics in developing countries have many patients with DSD who have not been seen early in life, but who have presented late, even in late adolescence or early adult life. These patients have survived infancy without medical help and so they do not have salt wasting CAH. Many of them have non-salt wasting CAH, XY partial gonadal dysgenesis, or other forms of XY DSD such as partial androgen insensitivity. By virtue of their late presentation, they are at risk for a number of problems in addition to having ambiguous genitalia: severe virilization giving an obviously different appearance; stigma and abuse; gonadal malignancy; hypertension (as in hypertensive forms of CAH); and gender identity disorder. A girl with untreated CAH becomes progressively more virilized and by the second decade, is likely to be starting to identify as male, even though the gender identity during earlier childhood was female. Transition to a male gender identity in these circumstances is quite common, even though the genitalia remain totally ambiguous. It is tragic when this happens, because any chance of fertility is lost if the individual grows up as a male.

There has been no research carried out on what should be the optimal management for DSD patients who present late. Decisions are made about genital surgery following consultation with the parents but not necessarily involving the child. Psychological evaluation to assess gender identity or the emotional state of the child, who may have been the butt of ridicule for years, is not offered. In an older child,

the psychology and gender identity should take precedence over physical characteristics.

### 6.8 A third sex?

G. Herdt, in his book, *Third Sex, Third Gender: Beyond Sexual Dimorphism in Culture and History* [31] takes an anthropological approach to explore the debate arising from proposals that society should create a special legal category for individuals who, for whatever reason, are unable to accept being identified according to the traditional categories of male and female. Some cultures are more accepting of than others in accepting people whose gender identity is somewhat ambiguous—for example Samoan culture permits some males to adopt female roles and to be honorably identified as *fa'afafine*, rather than as male or female. Generally, however, society has been strongly opposed to any suggestion of a third sex, although in some western countries, changes to legislation are being drafted to make any form of discrimination on the basis of sex, gender or religion illegal.

### 6.9 Immigrant health issues

Many big cities in western countries have rich cultural diversity as a result of post-war immigration. In some parts of Melbourne, for example, over half of the residents were born overseas. Waves of refugees who have come from war zones and economically challenged countries are now trying to blend into a society with strikingly different values from the ones they came from. Recognizing the need to cater for clients from backgrounds very different from the host country in terms of culture, education, language and economic status, hospitals and governments have made immigrant health a specialty in itself. In relation to DSDs, cultural differences are likely to be exposed in relation to gender preference and decisions about surgical intervention. Parents from Greek, Arabic, Chinese, Pakistani or Indian backgrounds, for example, prefer male babies and they will be very resistant to suggestions that a child with genitalia that appear more male than female (such as a 46,XX infant with congenital adrenal hyperplasia) should be raised female and have surgery to remove the valued 'male' parts.

### 6.10 The way forward

This paper has focused on differences between resource-rich and resource-poor countries in the presentation and management of patients with DSD. Poverty, affecting the patient and the family, as well as the medical system, the education system and the availability of social security, is the main factor underlying these differences and is a more important driver than religious belief or culture per se.



A great deal of assistance could be given by wealthy countries to accelerate the development of better conditions and better outcomes for patients with DSD in developing countries. Here are some proposals:

- At least one specialized DSD treatment centre including mental health services in every country
- Centralization of steroid laboratories within a country or region
- Development of paper-based blood and urine steroid analytical methods
- Development of an economical 17-hydroxyprogesterone assay designed for use in resource-poor countries without ready access to radioisotopes
- Focus on quality assurance programs in laboratories
- Collaborative development of algorithms to improve diagnostic capacity when resources are extremely limited
- A DSD Foundation to support the care of the poorest patients with DSDs
- A campaign to ensure that hydrocortisone and fludrocortisone are registered and available at the cheapest possible price in every country
- Programs to alleviate poverty: micro-finance, positive partnership programs to provide employment, advocacy at government level for the provision of social security
- Postgraduate educational programs designed to help health professionals in resource-poor countries to understand DSDs
- Internet-based mentoring to support continuing medical education
- More emphasis on genetics in the undergraduate medical curriculum
- International collaboration to help develop culturally appropriate educational materials suitable for parents and patients with limited education
- Community education through the mass media, both print and electronic, which is now accessible to the remote areas as well as the cities. More discussion programs to raise public awareness about DSD and services that are available should be encouraged.

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