

# Long-Term Outcome of Disorders of Sex Development

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## Key Words

Cultural difference · Disorders of sex development · Gender · Genital surgery · Gonadal cancer · Long-term outcome

## Abstract

The management of disorders of sex development (DSD) has been a problem area for years, partly because clinicians have started to see that not all of their patients grow up to be happy adults content with the gender assigned to them at birth, and partly because of the vigorous activities of patient advocacy organizations who have publicized their unhappiness and disagreement about current practices to the world at large and to politicians in particular. Results from a large number of long-term outcome studies have been published in the last decade and this paper attempts to give an overview of what we now know and what we still do not know about how to obtain a good outcome for our patients. Many studies have focused on a particular disorder and there have been more about congenital adrenal hyperplasia and complete androgen insensitivity (CAIS) than any of the other conditions, even though mixed gonadal dysgenesis is probably more common than CAIS. This is because researchers have wanted to know about the effects of hormones on the brain. There have been studies from a number of different countries, and cultural differences come to the fore in disorders affecting sex and gender. Very few studies have been done in Africa or East Asia so far. Long-term outcome should be studied in every treatment center, but there is a great

need for study instruments to be developed that would be robust enough to use in a range of different cultural settings and languages. The studies show that while many patients fare well and are leading productive lives, gender dysphoria has been underestimated in the past and that gender counseling as well as sexual counseling should be part of the multi-disciplinary service available to patients with DSD. More emphasis is also needed on strategies to prevent the development of germ cell cancers. Urological problems in both males and females with DSD have been underestimated and deserve more attention. Copyright © 2008 S. Karger AG, Basel

The long-term outcome of disorders of sex development (DSD) has been the subject of intense interest for decades. A report from the Dominican Republic [Imperato-McGinley et al., 1979] revealed that XY individuals with 5 $\alpha$ -reductase-2 deficiency were initially raised as females but underwent spontaneous transition to male gender identity during adolescence. Reports in the 1990s from Australia [Warne, 1992] and the United States [Meyer-Bahlburg et al., 1996] described girls with congenital adrenal hyperplasia who had become so virilized that they could no longer accept their female gender identity. The advent of the internet in the late 1990s [Warne et al., 1998] led to the establishment of patient advocacy organizations such as the Intersex Society of North America and the Androgen Insensitivity Support Group, some members of which became high-profile

critics of prevailing western medical practices in respect of DSD which advocated feminizing genitoplasty regardless of other factors, and defended keeping sensitive medical information hidden from patients and even parents. Their vigorous media campaigns were, however, based on the effect their condition was having on their lives as adults and were driven by passion. An indignant medical profession protested at being attacked in this way, but until that time, very few long-term outcome studies had been carried out to allow either side of the debate to speak with authority about numbers. The need for these studies became obvious. Most of the long-term outcome studies identified for this review were published after 2000.

What is the value of a well-designed long-term outcome study? It may provide evidence that an intervention was or was not beneficial for the patient. It provides a basis for prediction and is therefore useful when protocols are being revised. It yields information about the current situation of the patients and what their on-going needs are. It may reveal unforeseen events that occurred. It speaks about how a disorder continues to affect people's lives as they reach adulthood, middle age, and beyond. It might provide a reflection about the cultural context in which the study took place. It measures how well a particular treatment center is doing and may allow different centers to compare their results.

What is actually measured? The data will record selected aspects of the current situation of a cohort of patients, such as their physical health, mental health, social integration and status, sexual health, fertility, etc. It might record important events in the patient's journey and explore how the person managed threats as well as successes, devised strategies, used help that was offered, and identified things that were unhelpful or actually harmful.

What are the limitations? The report can only describe the participants in the study; non-participants keep their information to themselves and they could be different from those who participated. Studies of DSD never achieve 100% participation – patients die or are lost to follow-up, they are often unwilling to participate for various reasons, or they may be incapable of participating. The term DSD covers a wide range of conditions, many of which are rare, and conclusions from studies that attempt to consider them as one group may be different from those derived from studies of well-defined, disorder-specific groups. Long-term outcome depends on many factors that may or may not be related to the medical care that was provided, so in any particular study, the

results can really only reflect a whole package: it is difficult, if not impossible, to evaluate individual components of the overall therapy. Quantitative data may not capture the true essence of the problem and the question 'Why did some do better than others?' may need to be the subject of additional, qualitative research. Finally, the study may not be 'owned' by the group being studied and it may therefore not be looking in the areas that they would want studied (health professionals may want to find justification for what they did and may downplay the intense suffering of a small minority).

DSD have recently been re-classified and the new nomenclature [Hughes, 2008] will be used in this review.

#### **46,XX DSD**

##### *Congenital Adrenal Hyperplasia (21-Hydroxylase Deficiency) (CAH)*

The history of all women with classical CAH is of exposure to high levels of adrenal androgens in utero and of being born with ambiguous, even male genitalia, but also with ovaries and a uterus. They then typically had surgery during childhood to reduce the size of the clitoris and to divide the fused labia, allowing the vagina to open onto the perineum and removing any urinary obstruction that could have caused backfilling of the vagina. The hormonal management of CAH requires medications (a glucocorticoid and usually a mineralocorticoid) to be taken several times a day every day of their lives and regular attendance for medical reviews and blood tests. The parents were probably greatly distressed following the birth of their child; anxiety, guilt, embarrassment, and secrecy may have distanced them from family and friends.

Many long-term follow up studies of women with classical CAH have focused on the effects of prenatal exposure of the brain to androgens in genetic females. Gender role behavior is usually affected during childhood, sexual orientation is more often bisexual or homosexual than in the general population, but gender identity is rarely affected [Hurtig et al., 1983; Kuhnle et al., 1993; May et al., 1996; Kuhnle and Bullinger, 1997; Berenbaum et al., 2004; Long et al., 2004; Dessens et al., 2005; Meyer-Bahlburg et al., 2006]. Under certain circumstances, particularly when diagnosis is delayed and androgens are not adequately suppressed over a long period during childhood, gender identity may gradually change from female to male [Warne, 1992; Meyer-Bahlburg et al., 1996]. This is a well-recognized phenomenon in developing countries

where patients present late and due to both poverty, lack of education, and difficulty of access to essential medications do not achieve suppression of androgens in childhood [Armstrong et al., 2006; Gupta et al., 2006; Warne and Bhatia, 2006; Al-Maghribi, 2007]. On the other hand, gender reassignment from male to female in genetic females born with completely male genitalia is generally successful, provided that the correct diagnosis is made in early childhood and androgen suppression is maintained thereafter [Woelfle et al., 2002; Lee and Witchel, 2005].

Some authors have studied women with CAH to see if cognitive abilities are affected by prenatal androgen exposure, given that there were earlier reports that females with CAH had enhanced spatial orientation compared with non-exposed females. Females with CAH performed better than females without CAH and as well as males on targeting tasks but not on mental rotation tasks [Hines et al., 2003a]. Cerebral lateralization, as measured by hand preference and hearing tests, appeared to show a shift towards right hemisphere dominance in adolescents with CAH [Kelso et al., 2000]. Other authors, however, dispute these findings [Malouf et al., 2006] and report no consistent differences attributable to CAH.

Intense controversy has raged over the past decade about the ethics of performing genital surgery on infants unable to give consent. Critics of this practice argue that the surgery is unnecessary in an infant, given that the sole function of the clitoris is to give sexual pleasure. Because women with CAH nearly all had genital surgery as infants or young children, many studies focused on sexual function. All studies agree that women with CAH engage in sexual activity less frequently than women studied in control groups [Kuhnle et al., 1993, 1995; May et al., 1996], have greater degrees of pain and discomfort associated with penetrative intercourse [Warne et al., 2005a], are less fertile [Hagenfeldt et al., 2008], and have an increased risk of gestational diabetes [Falhammar et al., 2007]. Women being treated for CAH have circulating androgens that are lower than normal and higher progesterone levels [Helleday et al., 1993]; whether this could be related to alterations in libido is unknown. Reduced clitoral sensation is clearly a factor for some [Schober, 2004] as is restenosis of the introitus [Crouch et al., 2008]. The history of clitoral surgery and of the different types of operations used has been reviewed by Lean et al. [2007] and a startling recent discovery about the anatomy of the clitoris in normal women [O'Connell et al., 2005] raised questions about what the extent of the enlarged internal parts of the clitoris would be in women with CAH, and how this

would affect the woman. Removing a source of lower urinary tract obstruction, which because of urine backflow into the vagina can predispose to recurrent urinary tract infection, is used as a justification for early surgery to separate fused labia. Women with CAH are at a greater risk of lower urinary tract symptoms such as stress and urge incontinence than other women [Davies et al., 2005], but whether this is a consequence of surgery or their original anatomical disturbance, which can include a high junction between vagina and urethra, is unclear. A single report [Claahsen-van der Grinten et al., 2006a] drew attention to the risk of ovarian adrenal rest tumors in CAH. Testicular adrenal rest tumors are common in men but ovarian adrenal rest tumors in women are for some reason rare. Large myelolipomas in the adrenal glands can occur in adults with poorly controlled CAH. They are benign but can haemorrhage.

Women with CAH, particularly those with the salt-losing form, have reduced fertility [Claahsen-van der Grinten et al., 2006b]. One reason for this is polycystic ovarian disease [Hague et al., 1990]. Other reasons are the reduced frequency of sexual intercourse and also suppression of gonadotropin secretion by elevated serum progesterone levels.

Women with salt-losing CAH sometimes encounter a situation where suppression of hyperandrogenism requires a high dose of glucocorticoids, resulting in unacceptable side effects such as obesity, glucose intolerance, and hypertension. In this group, bilateral laparoscopic adrenalectomy has been advocated. Final judgment on this is reserved, but benefits in terms of enhanced fertility have been reported [Ogilvie et al., 2006]. Final height in treated adults is slightly shorter than target height but within the normal range [Nguyen et al., 2006], except in women who had non-salt-losing CAH, presented very late with an advanced bone age, and went into central precocious puberty following the commencement of glucocorticoid therapy; they have a much reduced final height.

Quality of life in women with CAH is impaired by psychosexual difficulties [May et al., 1996; Zucker et al., 1996; Wisniewski et al., 2004; Nordenskjöld et al., 2008], many of which should be preventable. This is clearly an area where a multi-disciplinary team approach to the management of adolescent patients is required, as well as well-prepared transition from pediatric to adult care. Support and guidance from a sexual health counselor (or the likes) would be of advantage. Girls with CAH are left to fumble through sexual difficulties themselves as there is no one properly qualified in the general multi-disci-

plinary setting to address the real issues. For young people this is the most important management aspect of CAH, but yet it is brushed over. Generally, health care professionals only consider whether the surgical outcomes are adequate for sexual intercourse. That is not entirely the problem. Minor degrees of clitoral enlargement do not require surgery and avoiding clitoral reduction wherever possible has been strongly advocated. For more detailed reviews, see Lee and Witchel [2002], Wiebke and Krone [2007], and Riepe and Sippell [2007].

#### *46,XX Congenital Adrenal Hyperplasia (11 $\beta$ -Hydroxylase Deficiency)*

This form of CAH accounts for 10% of all cases. It is associated with hyperandrogenism causing ambiguous genitalia in females, and the accumulation of mineralocorticoids which cause arterial hypertension. Long-term outcome depends on the success of the genital surgery carried out in childhood and control of blood pressure by glucocorticoid treatment [White and Speiser, 1994].

#### *46,XX Ovotesticular DSD*

In 60–82% of cases, the karyotype in human ovotesticular DSD is 46,XX [Wiersma, 2004; Verkauskas et al., 2007]. Others may be 46,XY, 46,XX/46,XY chimeras or have other karyotypes. The genital appearance ranges from normal male to normal female, but many have ambiguous genitalia. Both ovarian and testicular tissues coexist in the person, with the distribution of one vs. the other varying considerably between individuals [van Niekerk and Retief, 1981]. While an ovotestis may have two distinct poles, an even distribution throughout the length of the gonad is commonly seen. A normal ovary containing fertile oocytes is possible on one side (most commonly the left) with an ovotestis or dysplastic testis on the other, but the testicular element degenerates faster than the ovary and male fertility is rarely if ever possible. Testosterone production, however, may be adequate. The risk of gonadal malignancy is low unless a Y chromosome is present [Looijenga et al., 2007]. Female sex of rearing, which preserves the chance of fertility, has been the preferred option in many cases and in these, the testicular component is removed to prevent unwanted testosterone secretion and reduce the risk of malignancy [Damiani et al., 1997, 2005; Krstić et al., 2000; Verkauskas et al., 2007].

#### *46,XX Testicular DSD*

In this condition (formerly known as XX male syndrome), similarities to Klinefelter syndrome are very

strong, although men with 46,XX DSD are shorter than men with Klinefelter syndrome and men in the general population [Vorona et al., 2007]. The testes are dysgenetic and infertility is the rule. The *SRY* gene is expressed in some, but not all, affected individuals [Abusheikha et al., 2001].

#### *46,XX Mullerian Agenesis Syndrome*

While not associated with sexual ambiguity, the Mayer-Rokitansky-Küster-Hauser syndrome [Morcel et al., 2007] is in the spectrum of DSD. Typically, the uterus and vagina are absent but there is some variation in anatomy. The ovaries may be ectopic, sometimes even in the inguinal canal where they are mistaken for testes. Treatment of the vaginal hypoplasia does not always require surgery as the vagina is able to lengthen in response to stretching over time, as in regular and frequent sexual intercourse. While isolated cases of ovarian cancer have been reported, it is unclear if the overall risk is increased. Cancer in Mullerian duct remnants does not appear to be increased. Women with the condition have a range of emotional difficulties and benefit from professional counseling. At our center, patients have found a support group very helpful.

### **46,XY DSD**

#### *Complete Androgen Insensitivity Syndrome (CAIS)*

The experience of women with CAIS has been documented very eloquently by an international patient advocacy group (<http://www.aissg.org/>). In the past, the failure of doctors to disclose the true nature of the condition to them and their parents led to major difficulties and this has generated a great deal of anger and resentment. Partly, the non-disclosure was due to a paternalistic attitude but it was also due to the perceived difficulty of explaining XY chromosomes and testes to a girl without traumatizing her. This has now been overcome and full disclosure is now generally advocated and practiced within a more holistic, multi-disciplinary context with literature to support it [Warne, 1989; Lee and Money, 2004]. Gender identity is female [Hines et al., 2003b] and both breast size and body shape are normal. Pubic and axillary hair is scanty or absent. Women with CAIS have no uterus, and this affects body image and self-esteem, especially if combined with a degree of vaginal hypoplasia sufficient to make penetrative sexual intercourse difficult or impossible [Wisniewski et al., 2000; Wisniewski and Migeon, 2002; Minto et al., 2003]. Surgery is not always necessary as repeated attempts at intercourse can

effectively lengthen the vagina. There is however a number of surgical procedures that are used [Thomas and Brock, 2007]. The testes are usually in a superficial inguinal position and can be the size found in men, so that they are easily knocked or compressed against the body and can be very painful during sexual intercourse or sporting activities, or when wearing tight clothes. Sometimes this is the reason for choosing to have them removed. There is an increased risk of testicular cancer (seminoma), but this risk, once considered to be about 9%, is now thought to be of the order of 3% and only occurs after puberty [Skakkebaek, 1979; Handa et al., 1995; Sakai et al., 2000; Nojima et al., 2004; Hannema et al., 2006; Looijenga et al., 2007; Robboy and Jaubert, 2007]. Current recommendations would support leaving the testes in until after puberty has been completed and then either removing them (with oestrogen replacement) or instituting a careful monitoring process for the early detection of seminoma. Detected early, seminoma can be effectively treated and has a good prognosis. Intra-abdominal testes must be removed. However, many women with CAIS have had their testes removed when they were children as this is still common practice.

Women with CAIS have an increased risk of osteoporosis whether or not they have their testes [Soule et al., 1995; Bertelloni et al., 1998; Mizunuma et al., 1998; Sobel et al., 2006; Danilovic et al., 2007]. Although adult circulating testosterone levels are high (about 50 nmol/l) if the testes have not been removed, the skeleton is unresponsive to testosterone and consequently bone mineral density is estrogen dependent. Estrogen levels in women with CAIS are higher than in men but lower than in women with ovaries. Therefore it is possible, though as yet unproven, that women with CAIS who have their testes would benefit from treatment with additional estrogen to prevent osteoporosis [Warne et al., 2005b].

Women with CAIS, being XY, are candidates for red-green color blindness, a disorder otherwise confined to males, and they are on average slightly taller than average women. Being an X-linked trait, CAIS may affect sisters, aunts, and other female relatives.

#### *Partial Androgen Insensitivity Syndrome (PAIS)*

PAIS is associated with great phenotypic diversity and the phenotype is poorly predicted from the genotype [Deeb et al., 2005]. Within one family (the condition is inherited as an X-linked trait), it is possible for some individuals to have ambiguous genitalia and for others to have a micropenis (without hypospadias) and gynaecomastia. Thirty years ago, doctors were taught never to

consider male sex of rearing in a child with ambiguous genitalia if it was due to androgen insensitivity, on the basis that the penis would not grow at adolescence and therefore life would be intolerable. This was an exaggeration of the true situation [Husmann, 2004; Lee and Houk 2004]. This policy led to great unhappiness for those who had feminizing surgery and then developed with a male gender identity [Mazur, 2005]. One study has reported that nearly 25% of subjects with PAIS were dissatisfied with their adult gender identity, regardless of whether they had originally been assigned male or female [Migeon et al., 2002a]. It should be noted, however, that in the majority, gender identity followed the sex of rearing. The policy about genital surgery in babies and children with PAIS remains controversial. Some patient advocacy groups have called for the banning of early genital surgery, preferring to allow individuals to decide for themselves when they are old enough. We now advocate a male sex of rearing in cases of PAIS because it preserves choice, even though the surgery to create a penile urethra is much more technically difficult than feminizing genitoplasty. High dose testosterone therapy [Grino et al., 1989] has potential for enlarging the penis.

The risk of testicular cancer is high (55%) in intra-abdominal testes of males with PAIS [Hughes et al., 2006] and therefore excision is recommended. The risk for scrotal testes is considered to be lower, but still moderately high, so if they are retained, a clearly communicated risk management strategy is essential. This would involve 6-monthly palpation, biopsy looking for carcinoma in situ (CIS) after puberty, and either removal of the testis or irradiation if CIS was found. Retention of testes would be expected to be associated with the development of adolescent gynaecomastia which might require bilateral mastectomies.

#### *5 $\alpha$ -Reductase-2 Deficiency*

As first described [Imperato-McGinley et al., 1979], 5 $\alpha$ -reductase-2 deficiency causes a gradual gender identity change from female to male at puberty in a significant number of individuals, if the testes have been retained and not removed in early childhood [Cohen-Kettenis, 2005a]. This has made it difficult to define a policy suitable for all environments [Houk et al., 2005]. Gynaecomastia does not develop. The adult penis is small. Dihydrotestosterone treatment has been given with encouraging results in children [Charmandari et al., 2001]. The risk of testicular cancer appears to be relatively low. The pattern of inheritance is autosomal recessive.

### *17 $\beta$ -Hydroxysteroid Dehydrogenase Deficiency*

17 $\beta$ -hydroxysteroid dehydrogenase deficiency, like 5 $\alpha$ -reductase-2 deficiency, causes a transition in gender identity from female to male in some individuals [Rosler, 2006], but the response to administered testosterone would be greater. The phenotype is only seen in genotypic males; affected females have no symptoms. The pattern of inheritance is autosomal recessive.

### *46,XY Lipoid Adrenal Hyperplasia and 46,XY 17 $\alpha$ -Hydroxylase Deficiency*

These two forms of CAH are both extremely rare. Lipoid adrenal hyperplasia, caused by a deficiency of the steroid acute regulatory protein (StAR), is associated with a complete block in steroid hormone secretion by both the adrenals and the testes, so that all subjects, whether XX or XY, have a female phenotype [Miller, 2007]. The prognosis is good, once the diagnosis has been made and treatment started with both a glucocorticoid and a mineralocorticoid. Estrogen replacement is needed to induce puberty and is continued life-long. The testes secrete Mullerian inhibitory substance (MIS) normally and therefore there is no uterus.

17 $\alpha$ -hydroxylase deficiency [Kater and Biglieri, 1994] also results in a female phenotype in genotypic males, and there is no uterus, but unlike lipoid adrenal hyperplasia, it is associated with glucocorticoid-suppressible hypertension due to the accumulation of mineralocorticoid precursors.

### *46,XY Complete Gonadal Dysgenesis (Swyer Syndrome)*

Women with 46,XY complete gonadal dysgenesis differ from women with CAIS in that spontaneous breast development at adolescence does not occur. Serum FSH and LH levels are high, due to primary gonadal failure. Hormone replacement therapy is able to induce secondary sex characteristics including menses, because women with this condition have a uterus. It is possible for them to carry a pregnancy if an embryo is implanted into the uterus and appropriate hormonal support is administered. The streak gonads carry a high risk of cancer and should always be excised. Gender identity is female [McCarty et al., 2006].

### *46,XY Partial Gonadal Dysgenesis (GD)*

The 46,XY form of partial GD is quite rare but is the subject of considerable interest to basic researchers into the genetic regulation of gonadal differentiation, who are now applying new gene discovery strategies including

micro-array. Patients are highly sought-after for this reason. More commonly, partial gonadal dysgenesis is associated with a 45,X/46,XY mosaic karyotype and discussion about long-term outcome will be found later in this paper.

### *Persistent Mullerian Duct Syndrome*

There are no long-term outcome studies on this very rare condition which is due either to mutations in the gene for Mullerian inhibitory substance (MIS) or in the MIS receptor gene. The usual anatomy is that the two vasa deferentia are enclosed within the lateral walls of the uterus and the testes are found in inguinal hernias. Removal of the uterus is contraindicated because it destroys any chance of spontaneous fertility.

### *46,XY Cloacal Exstrophy*

Genetic males with cloacal exstrophy have normal testes but the penis is severely hypoplastic, even absent. A generation ago, they would have had their testes removed and female genitalia constructed, then raised female. The long-term outcome was disastrous; most of those treated in this way grew up with an unequivocally male gender identity [Reiner and Gearhart, 2004].

## **Sex Chromosome DSD**

### *45,X/46,XY Partial Gonadal Dysgenesis*

This condition, often referred to as mixed gonadal dysgenesis, is one of the two most common causes of ambiguous genitalia and until 1990, most endocrinologists thought that it was invariably associated with ambiguous genitalia, which is far from true. Follow up of 92 patients in whom this karyotype had been detected by antenatal testing revealed that 95% had a normal male phenotype and of these, 27% had abnormal gonadal histology [Chang et al., 1990]. The risk of malignancy in the group with male phenotype remains unclear; a strategy has been proposed for management, involving close monitoring and testicular biopsies after puberty has been completed [Müller et al., 1999].

Endocrinologists and surgeons are familiar with the 5% of 45,X/46,XY fetuses who are born with ambiguous genitalia and who represent just under half of all babies with ambiguous genitalia. There is considerable phenotypic variation, but the most common gonadal phenotype would be of a testis on one side and a streak gonad on the other [Telvi et al., 1999]. Ovotesticular DSD is also part of the spectrum. Streak gonads which are intra-ab-

dominal carry a high cancer risk and should always be removed. The scrotal testis is also dysgenetic and it too has a high risk of cancer, but patients raised male want to keep the testis if possible and therefore need close monitoring by palpation, ultrasound, and biopsy carried out at appropriate times. A uterus is present in 75%, and because of this, the female sex of rearing may have been chosen to allow the possibility of having a baby through assisted reproductive technology. Turner features are found in some individuals. Others have short stature and are considered for growth hormone therapy [Richter-Unruh et al., 2004]. More often than not, gender identity in adulthood conforms to the sex assigned at birth [Cohen-Kettenis, 2005b; Warne et al., 2005a; Szarras-Czapnik et al., 2007] but psychological outcomes for males appear to be slightly better than for females. Males born with perineal hypospadias, however, have more long-term urological problems, which reflect the difficulty of constructing a penile urethra from tubes constructed from skin, joined end to end [Warne et al., 2005a].

#### *47,XXY Klinefelter Syndrome with Genital Ambiguity*

Although genital ambiguity is not usually a feature of Klinefelter syndrome, it does occur [Lee et al., 2007] and can be associated with gender dysphoria.

### **Discussion**

In preparing this review, I asked several people who have lived with a DSD all their lives how they would define a good long-term outcome. A middle-aged woman with AIS replied: 'Feeling at home in one's body, at peace with oneself as a whole person, happy to have been born/created, satisfied with HRT (hormone replacement therapy) if it has been necessary, to be able to enjoy sexual relations should one desire to enter into them, positive view of medical intervention received over the years, or with the process and results of coming to terms with the trauma.' A man born with ambiguous genitalia due to a form of CAH commented: 'It has taken me years to feel comfortable with the body I have today. I don't really feel at home. I am a guest who has learned to make myself comfortable in someone else's house but I will never be the one who owns this home. It is a house but not a home.' From these statements, it appears that perceptions of self, body image, identity, sexuality, comfortable with the appearance of the body, relationships with partners and with the medical profession, and a sense of being valued in their social contexts are all markers of a good long-term outcome.

The scientific studies that have been conducted have tried to measure qualities like body image, satisfaction with the body and the genitalia, sexual feelings and sexual activity, general health, mental health, and broadly, quality of life. They reveal that the quality of life for many people with DSD, while not perfect, is satisfactory or good. There has been a much greater recognition in the last 10 years that many young people with DSD grow up not feeling comfortable in their bodies; in particular, they are not sure about their gender identity. A small percentage of these are ultimately unable to accept the gender they grew up in, and they take action to change it. Counseling about gender has to become a part of the service provided to every DSD patient after puberty.

Little information is available about how to help people born with atypical genitalia to build the self-esteem needed to establish healthy intimate and sexual relationships. A middle aged woman with complete AIS disclosed to a group of similarly affected women that in her youth, the question that had troubled her most was 'Would there be someone out there to love me?' It is therefore not enough for long-term follow up studies to focus on the particular, e.g., clitoral sensation without asking questions about the existential position of the whole person. 'This can't be emphasized enough. People can have had excellent surgical outcomes and very good pathology results throughout their lives, but still have psychologically difficulties. We live with the knowledge that we produce too much testosterone but do not know to what extent the testosterone has had an impact on our outward appearance and how visible this is to people around us (i.e., if we hadn't been born with CAH or other DSD what would we have looked like physically, not just considering genitalia)' [Claire Henderson, personal communication].

Disorders of sex development present many challenges for people living with the conditions, their parents, and the health professionals who care for them [Slijper et al., 1998; Thyen et al., 2005]. It is an advance that so many centers are reporting long-term outcome data and the fact that these reports are not only from centers able to devote a high level of human and technical resources, but also from very poor countries with very different cultural beliefs and traditions [Ammini et al., 2002; Warne and Raza, 2008], is a great advance. It is clear that while outcomes in the technically advanced and better resourced countries are still far from perfect, they are dramatically better than in developing countries where services and medicines are in restricted supply, poverty and lack of education are widespread, and rumor and discrimination, based on ignorance, make people's lives a misery.

Many patients in developing countries are not given any treatment or counseling at all. There is a strong preference for male children in some countries and females born with genital abnormalities have a much lower chance of survival than males. 'Parents prefer the intersex children to be reared as male possibly because of the less social stigma attached to an impotent male than to sterile female, and because males are socially independent' [Rajendran and Hariharan, 1995].

Within living memory, similar conditions prevailed in western societies and the degree to which progress has been made in the development of a holistic and collaborative approach to the management of DSD, built on great scientific advances, should be acknowledged. Patient advocacy groups should be proud of the positive influence they have had on the debate. Their relationships with the medical profession have improved greatly since they were established in the late 1990s and a healthy dialogue has developed.

Many long-term outcome studies [Rajendran and Hariharan, 1995; Migeon et al., 2002a, b; Mazur et al., 2004; Reiner, 2005; Warne et al., 2005a; Johannsen et al., 2006; Julka et al., 2006; Nihoul-Fékété et al., 2006; Brinkmann et al., 2007; Jürgensen et al., 2007] have looked at mixed groups of DSD subjects, based on the premise that everyone desires a good quality of life and therefore it is reasonable to study all of the patients treated in one insti-

tution as a single group, regardless of the different diagnoses, using very broad outcome measures [which have been reviewed by Zucker, 2005]. Only a few [e.g., Warne et al., 2005a] have included a control group.

The management of DSD requires a multi-disciplinary team approach, properly funded and working from a strong evidence base. Ideally, patient advocacy groups should be involved, and where relationships between local practitioners and local support groups have become frayed, mediation to achieve compromise and positive engagement would be helpful. More research into basic mechanisms of sex differentiation, the determinants of gender identity, and epidemiology is needed. Highly specialized diagnostic facilities should be centralized within countries and even regions, with provisions made to subsidize testing for the poorest of the poor. International collaborations to generate sufficient numbers for the study of very rare disorders are being established and should provide better information on which to base new management protocols.

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