Chapter 11
Gender and Sexuality in Disorders/Differences of Sex Development

Baudewijntje P. C. Kreukels and Tim C. van de Grift

Abstract Intersex conditions or disorders/differences of sex development (DSD) are conditions in which the development of chromosomal, gonadal and/or genital characteristics is atypical. Studies in individuals with DSD conditions may provide valuable insights on the roles played by sex chromosomes, sex hormones, sex anatomy and gender of rearing in the development of gender role and gender identity. An overview is given regarding various aspects that may be influenced in individuals with DSD conditions: play behaviour, activities, interests, cognitive functioning and brain development. Furthermore, we will highlight gender development across the DSD spectrum by describing the literature regarding gender identity and expression in individuals with DSD conditions. Gender dysphoria and gender change are more prevalent in individuals with DSD conditions. These findings have also been important in the debate around gender assignment in individuals born with ambiguous genitalia. In addition, we will describe sexual development, as sex-atypical physical appearance, hormone replacement therapy, past surgical interventions, and psychological issues may all affect sexuality. Recent developments show there is more room for gender diversity in society. A less binary approach to gender may also positively influence feelings regarding gender in variations of sex development.

Keywords Disorders of sex development · Differences of sex development · Intersex conditions · Gender role behaviour · Gender identity · Gender expression · Gender assignment · Gender dysphoria · Gender development · Sexual development

B. P. C. Kreukels (✉) · T. C. van de Grift
Department of Medical Psychology, Center of Expertise on Gender Dysphoria, Amsterdam University Medical Center, Amsterdam, The Netherlands

Department of Plastic, Reconstructive and Hand Surgery, Center of Expertise on Gender Dysphoria, Amsterdam University Medical Center, Amsterdam, The Netherlands
e-mail: b.kreukels@amsterdamumc.nl

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In typical sexual differentiation, development of chromosomal, gonadal and anatomical characteristics are in line. Congenital conditions in which the development of these characteristics is atypical are labelled as intersex conditions or disorders/differences of sex development (DSD). There is a lot of debate with regard to terminology, and various terms are being preferred for various reasons by various stakeholders, while considered offensive by others (see Johnson et al., 2017; Miller et al., 2018). In this chapter, we will use DSD conditions, being aware of the difficulties regarding this terminology, but going with the term that is still widely used in both the medical and public arena that covers a wider range of conditions than intersex. In such conditions, genital sex may not correspond to gonadal or chromosomal sex. Gender (identity and role), in such cases, may be congruent with genital sex, but not with chromosomal or gonadal sex. In other cases, gender may be incongruent with genital sex.

In his work with children with DSD conditions, John Money proposed the distinction between sex and gender (Money, 1994). In addition, he introduced the concepts of gender role and gender identity, with gender role being the public expression of gender identity and gender identity the private manifestation of gender role. Studies in individuals with DSD conditions play a key role in attempts to understand the development of gender role and gender identity, as they often provide valuable insights on the role sex chromosomes, sex hormones, sex anatomy and nurture play (separately or in varying combinations).

In typical sexual differentiation, the male-typical pathway starts off with XY chromosomes. The sex determining region Y (SRY) gene on the Y chromosome induces the development of the testes, and the testes produce testosterone, which triggers the development of male genitalia. Generally, these persons are reared as males, live in the male gender role and have a male gender identity. In individuals with XX chromosomes, ovaries develop in the absence of the SRY gene. Without exposure to testosterone from the testes, the genitalia and body develop in the female-typical direction. With female rearing, and living in the female gender role, the majority of women have a female gender identity. In individuals with DSD conditions, sexual differentiation is atypical and steps in this cascade of events may turn out differently (see Table 11.1 for a description of some of the most prominent DSD conditions) (Hughes et al., 2006; Lee et al., 2006, 2016).

Sex hormones play a crucial role in sexual differentiation. For example, people with XY chromosomes and complete androgen insensitivity syndrome (CAIS) do have testes, but are insensitive to testosterone and their body further develops in the female direction (although developing no uterus and deep vagina due to regression of Müllerian structures). Although a condition named congenital adrenal hyperplasia (CAH) does not seem to affect sexual differentiation in XY individuals, the exposure to elevated levels of testosterone during prenatal development in individuals with XX chromosomes with this condition may result in virilised genitalia, but also more male-typical behaviour and interests. These latter outcomes are ascribed to prenatal effects of sex hormones on the sexual differentiation of the brain, and called organising effects (Bakker, 2019; Phoenix et al., 1959). Effects of sex hormones during life on the already organised neural system are referred to as activating effects.

Table 11.1 Some of the more prominent DSD conditions, adapted from Hughes et al. (2006) and Lee et al. (2006, 2016)

Type	Examples
Sex chromosome DSD	45,X (turner syndrome) 47,XXY (Klinefelter syndrome) 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
46,XY DSD	Conditions of gonadal (testicular) development (complete and partial gonadal dysgenesis, ovotesticular DSD) Conditions of androgen synthesis or action (complete and partial androgen insensitivity syndrome [CAIS and PAIS], 5α-RD-2 deficiency, 17β-HD deficiency) Other (severe hypospadias, cloacal extrophy)
46,XX DSD	Conditions of gonadal (ovarian) development (gonadal dysgenesis, ovotesticular DSD) Conditions of androgen excess (21-hydroxylase deficiency: Congenital adrenal hyperplasia [CAH]) Other (cloacal extrophy, vaginal atresia)

Animal studies have been used to study such organising and activating effects of sex hormones (e.g. Hines, 2009, p. 1869–1909). In humans, these effects are difficult to study in typical sexual differentiation, because chromosomal, gonadal, hormonal, genital, and gender development are generally in line. But such effects can be studied in individuals with DSD conditions, where sexual differentiation during prenatal development is atypical.

Neurobiological studies into sex differences have for long mainly focused on sex hormone effects (either induced early in development or by measuring sex hormone levels at the time of study), but more recently attention has been given to the effects of sex chromosomes and the direct effects of genes on sexual differentiation of brain and behaviour as well (McCarthy et al., 2012). It should be noted that every cell in the body carries sex chromosomes. In animal studies, the four core genotypes model has been developed to study direct effects of sex chromosomes. This model makes use of genetically modified mice and the fact that the SRY gene causes the development of testes: 1.) XX without SRY (ovaries); 2.) XY without SRY (ovaries); 3.) XY with SRY (testes); 4.) XX with SRY (testes). By comparing type 1 and 2, one can distinguish effects of sex chromosomes, because the groups differ by XX and XY, yet their gonadal type is the same. By comparing type 2 and 3, one can distinguish effects of gonadal type (with effects of hormones as produced by the gonads), because they are different and sex chromosomes are similar. A human model for sex chromosome effects is provided by XY women with CAIS: Similarities with control men (XY) would indicate dominant effects of sex chromosomes.

11.1 Play Behaviour, Activities and Interests

Sex differences in play behaviour have been consistently reported, with boys preferring toys like vehicles, engaging in rough and tumble and preferring other boys as playmates more than girls do (Davis & Hines, 2020; Hines, 2011a). With the

relatively large sex differences and early-life assessment during a period of hormonal rest (hormonal levels are low from several months after birth until the early stages of puberty), play behaviour offers an easy way to examine effects of prenatal hormones on this parameter of gender development. Multiple studies in girls with 46,XX CAH, who have been exposed to increased androgen levels prenatally, have reported that they show increased preferences for male-typical toys on average (Hines, 2011b). Effects have been found across various measures, such as observation and self-report (Berenbaum & Meyer-Bahlburg, 2015). Because these girls have a possibly life-threatening medical condition and are sometimes born with virilised genitalia, it has been argued that other aspects than the exposure to elevated androgen levels may have led to increased male-typical behaviour and interests (Steensma et al., 2013). Parental influence on sex-typical behaviour in girls with 46,XX CAH has been studied. In laboratory observations, parental encouragement of sex-typical toy play did not seem to override the preference for male-typical toys in girls with 46,XX CAH (Pasterski et al., 2005). A subsequent study (Wong et al., 2013) showed that parents reported encouraging more male-typical toy play in girls with 46,XX CAH, possibly as a response to their increased interest in male-typical toys. Studies of offspring from women with normal variability in testosterone during pregnancy also show an association between maternal T levels in amniotic fluid and male-typical play preferences in their daughters (Hines, 2011b), although this association has been called into question (Davis & Hines, 2020).

More recently, it has been found that girls with 46,XX CAH show changes in processes related to self-socialisation of gender-related behaviour with lower responsiveness to cues that certain objects are female-typical (labelling) and less imitation of female models choosing particular objects (modelling) (Hines et al., 2016). The authors suggest therefore that prenatal androgen exposure not only affects gender-related behaviour by permanent changes in the brain, but also by changing processes involved in self-socialisation of gendered behaviour.

More male-typical interests, activities and occupations have been reported in women with 46,XX CAH as well, thus suggesting that masculinised traits continue into adulthood (Wisniewski & Aston, 2015), where “masculine” refers to traits and behaviour that are on average more prevalent in boys and men. However, XX women with CAH reported more feminine/less masculine patterns of gender role with age and were indistinguishable from XY women with CAIS in adulthood in this latter study, suggesting that other factors may become more important with age in the expression of sex-(a)typical patterns. Girls and women with CAIS report female gender role from childhood to adulthood (Wisniewski & Aston, 2015). In a study in individuals with various 46,XY DSD conditions raised either male or female, gender role increasingly corresponded with assigned gender throughout development into adulthood (Pappas et al., 2008). Socialisation, learning and endocrine influences may all contribute to this development. Recalled childhood gender role behaviour and gender identity/gender dysphoria (i.e. psychological distress resulting from the incongruence between their experienced gender and sex-specific bodily appearance) were studied in individuals with various DSD conditions (46,XY DSD, 46,XX CAH) with either typical or atypical genitalia and that were raised either male or

female (Callens et al., 2016). The authors concluded that although prenatal androgen exposure was shown to have large effects on gendered preferences in play and activities, gender of rearing appears to predict contentedness with gender identity better (Callens et al., 2016).

11.2 Cognitive Functioning

Although there are often more differences within sexes than between sexes with regard to cognitive functioning (Hyde, 2014), there are some abilities that tend to show differences between men and women. Men generally outperform women on certain visuospatial tasks, whereas women are superior in verbal fluency tasks (Halpern, 2012). Girls with 46,XX CAH seem to have somewhat better spatial abilities than their unaffected sisters (Berenbaum et al., 2012) and women with the most severe form of 46,XX CAH (and highest expected exposure to prenatal androgen) had similar performance to control men (both healthy and with 46,XX CAH) on a spatial task (Mueller et al., 2008).

Theory of Mind (ToM), the ability to form ideas about and make sense of other's and one's own perspectives on situations and events, has been studied in individuals with DSD conditions as well (Khorashad et al., 2018a). Women are reported to outperform men on ToM measures (Baron-Cohen et al., 2001; Khorashad et al., 2015). Birth-assigned females with 46,XX CAH or with 5α-RD-2 (both groups are exposed to high levels of testosterone during prenatal development) and age-matched control men scored significantly lower on a Reading the Mind in the Eyes Test (RMET, a ToM task) compared with individuals with low prenatal testosterone exposure/effects (age-matched control women, women with CAIS). Also, current testosterone replacement was associated with lower Reading the Mind in the Eyes Test scores. These findings suggest that karyotype (sex chromosomes) affects ToM performance to a lesser extent than prenatal hormonal levels, because both control women with XX karyotype and women with CAIS with XY karyotype perform better than control men with XY karyotype and women with CAH with XX karyotype.

11.3 Brain Development

Neuroimaging studies in individuals with DSD conditions have mainly been performed in women with CAIS and 46,XX CAH. The aim of such studies in women with CAIS is to determine if certain brain measures are influenced by hormonal action and/or by chromosomal pattern. Similarities between women with CAIS and control men would suggest chromosomal influence, whereas similarities between women with CAIS and control women would indicate hormonal influence on these measures. With regard to structural measures in women with CAIS, it is

found that their white matter Fractional Anisotropy values (Diffusion Tensor Imaging) are more similar to those of control women and different from those of control men (Savic et al., 2017; van Hemmen et al., 2016), suggesting that structural connectivity is primarily under the influence of hormonal action. For Cortical Thickness (CTh) the findings are more mixed; CTh in parietal and occipital cortices and the left temporal cortex in women with CAIS is in the female range, whereas CTh in pre (motor cortex) and postcentral gyrus (somatosensory cortex) is in the male range (Savic et al., 2017). Interestingly, when multivariate pattern recognition is used, women with CAIS were more similar to control men using grey matter or multimodal information as classifier (van Hemmen, 2017, p. 102). In structural development of the brain, both sex hormones and sex chromosomes may thus play a role, with a more dominant role for sex hormones (primarily testosterone) on white matter measures and other measures moderated by sex hormone and sex chromosome effects.

In functional neuroimaging, patterns in women with CAIS do seem to be more in line with control women in activation while viewing sexually arousing stimuli (Hamann et al., 2014) and while performing a mental rotation task (van Hemmen et al., 2014). This similarity is generally assigned to the effects of sex hormones because, again, women with CAIS, being insensitive to testosterone, display a female-typical instead of a male-typical pattern. However, it should also be noted that these women generally live in the female role and socialisation effects can also play a role in these patterns.

Studies in individuals with CAH have mainly focused on the amygdala. Grey matter volume is larger in bilateral amygdalae in men compared with women (Ruigrok et al., 2014). Decreased amygdala volume was observed in boys with CAH and girls with CAH compared to controls (Merke et al., 2003; Rose et al., 2004). In functional MRI studies, amygdala activation to negative facial expressions in women with 46,XX CAH was more similar to control men (Ernst et al., 2007); hypoactivation of the amygdala was observed in adolescent girls with 46,XX CAH and hyperactivation of the amygdala in adolescent boys with CAH during an emotional memory task (Mazzone et al., 2011). As the amygdala is abundant with androgen and oestrogen receptors, these findings are often discussed in the light of the exposure to sex hormones, but the imbalance of glucocorticoids in individuals with CAH should also be taken into account (Bramble et al., 2017), because the imbalance in glucocorticoids also appears to reduce amygdala volume.

11.4 Gender

As aforementioned, measures of gender expression, gender role behaviour and a range of gender-related psychological domains (e.g. cognitive abilities, social interests and personality traits) have been associated with sex hormonal variances in individuals with DSD conditions (Berenbaum & Meyer-Bahlburg, 2015). Empirical research shows that in individuals with DSD conditions, chromosomal, but mostly

hormonal and physical variations of sex influence the development of gender role as well as identity (Berenbaum & Meyer-Bahlburg, 2015). Sex hormones, of which androgens most strongly, impact structural brain development in early life (organisational effects) as well as exert temporary functional effects (i.e. activational) during puberty and adolescence. Clinical findings generally conclude that exposure to androgens is associated with more male-typical behaviour and identification (Bakula et al., 2017; Khorashad et al., 2018b). In cross-condition comparisons, women with DSD conditions characterised by more androgen exposure, such as women with 46,XY 5α-reductase deficiency and 46,XX CAH, score more masculine than control women on pre-school activities for example.

Historically, many of the medical and psychological treatments of individuals with DSD conditions have been motivated to facilitate sex-typical (i.e. in line with the assigned gender) gender development. In a relatively small subgroup of individuals with DSD conditions, gender assignment at birth is challenging due to ambiguity of the new-born's genitalia (e.g. in strongly virilised children with 46,XX CAH, or in undervirilised children with 46,XY conditions with partial androgen availability and/or sensitivity). For some DSD conditions, gender identification later in life is fairly predictable, while in other DSD conditions, development of gender identity and expression is difficult to predict a priori (Bakula et al., 2017; Fisher et al., 2016). The current global consensus guideline states "Factors that influence gender assignment include the diagnosis, genital appearance, surgical options, need for life long replacement therapy, the potential for fertility, views of the family, and sometimes the circumstances relating to cultural practices.", highlighting the complexity of these decisions (Lee et al., 2016). Still, the topic of gender development reaches beyond the group with genital ambiguity at birth; a substantial group of individuals across the DSD spectrum faces issues with gender identity ambiguity, sex-atypical physical appearance and deviance from societal norms (e.g. Brunner et al., 2016; Kreukels et al., 2018).

11.4.1 Gender Identity and Expression

While gender identity refers to the self-identification as female, male, or another gender (e.g. genderqueer, non-binary), gender expression relates to the social manifestation of gender, including clothing, preferences in peers or activities and gender role behaviour. Gender expression is often measured as more masculine/male-typical versus more feminine/female-typical (Bakula et al., 2017; Cohen-Kettenis, 2010).

Most studies examining development of gender identity and expression have been conducted in individuals with CAH (Berenbaum et al., 2018; Pasterski et al., 2015) or with 46,XY conditions (Wisniewski, 2012). In women with CAH (46,XX), around 95% is observed to develop a female gender identity during childhood and adolescence (Bakula et al., 2017). In individuals with a 46,XY condition, including complete gonadal dysgenesis or CAIS, individuals with female appearance at birth

(due to absent androgen action) almost exclusively identify as female later in life (Kreukels et al., 2018; Wisniewski, 2012). In individuals with 46,XY and genital ambiguity (e.g. in partial gonadal dysgenesis or 5α-reductase deficiency) both male and female gender identity development have been described (Wisniewski, 2012). In both the 46,XX CAH and 46,XY groups, masculine identification is associated with virilisation at birth (Apóstolos et al., 2018; Chowdhury et al., 2014; Pasterski et al., 2015). Historically, many studies have taken a relatively binary approach to assessing gender identity at follow-up, resulting in the aforementioned fairly homogeneous groups (male vs. female). Recent studies, however, have shown great variability in gender identification in all DSD subgroups (Brunner et al., 2016; Kreukels et al., 2018), describing adults with DSD conditions identifying outside the binary spectrum (including identifying as open, inter, or other). This may partly be due to a more non-binary or/and qualitative approach of studying gender identity. Additionally, discrepancies between self-reported (larger gender variance) and clinician-reported gender identity outcomes (more binary) have been observed (Kreukels et al., 2018). This possibly directs towards some threshold for individuals with DSD conditions to disclose their non-binary gender identities to clinicians.

Studies on gender expression in individuals with DSD conditions show great variance within and between subgroups and controls (Callens et al., 2016; Jürgensen et al., 2013; Khorashad et al., 2018b). Yet, across studies, gender expression was shown to be substantially influenced by sex hormone (mostly androgens) exposure (Wisniewski, 2012), and possibly associated with genotype variations as well (Frisen et al., 2009). Khorashad et al. (2018b) observed that across the DSD spectrum, in individuals with conditions with more virilisation (regardless of karyotype), more male-typical pre-school behaviour was observed. For girls with 46,XX CAH, multiple studies have observed more male-typical peer- and activity-preferences, compared with girls without CAH and attributed this finding to the increased androgen exposure (e.g. Berenbaum et al., 2018; Pasterski et al., 2011). Little research on gender expression in individuals with 46,XY conditions has been conducted and findings vary per specific diagnosis and level of virilisation (Wisniewski, 2012).

Apart from hormonal exposure, several other factors have been studied in relation to development of gender expression in individuals with DSD conditions, including parental characteristics and surgical treatments (e.g. Khorashad et al., 2016), although smaller effect sizes of these factors are generally reported, as compared to those of hormonal effects. Parents can effectively influence children's gender development through parental modelling as well as actively reinforcing/discouraging gendered behaviour (Wisniewski & Sandberg, 2015). Parental attitudes were shown to impact the approach they take towards gender (a)typical behaviour in individuals with DSD conditions (Joseph et al., 2017; Khorashad et al., 2016). These studies from Iran and India both reported that conservative parental attitudes were strongly associated with negative and corrective approaches towards gender-atypical behaviour. Family views on males and females also influenced the likelihood of gender change later in life. The long-term effects of (early) genitoplasty surgery have not been studied in a controlled design; however, the few descriptive studies

available show both (1) a low incidence of gender reassignment or reverse surgery, and (2) relatively frequent feelings of abnormality, body image issues and sexual difficulties despite genital surgeries, which was reported across multiple DSD conditions (Callens et al., 2012; Lee et al., 2016; van de Grift et al., 2018). Regarding these persistent feelings of abnormality, surgical "normalisation" of genitalia may not secure binary gender identity development and could still result in individuals exploring alternative gender expressions.

11.4.2 Gender Assignment

In case of gender assignment in a new-born with genital ambiguity, recent consensus statements advocate a shared decision-making approach, taking long-term outcome data, clinical evaluation and parents' preferences into account (Lee et al., 2016). A recent study by Timmermans et al. (2019) revealed how clinical decision-making on gender assignment is a complex process in which both clinicians and parents anticipate the child's future gendered being, including sexual intimacy, fertility, gender dysphoria, stigma, and gonadal cancer risk (Timmermans et al., 2019). While much emphasis in clinical support for individuals (and their families) with DSD conditions is put on gender assignment and development, other scholars advocate for an approach beyond gender only, with more focus on psychosocial functioning and quality of life (Wisniewski & Sandberg, 2015).

As mentioned earlier, gender assignment is strongly influenced by long-term studies on development of gender identity and expression studied per clinical diagnosis, level of virilisation, genetic mutation, etc. (Chowdhury et al., 2014; Lee et al., 2016). Importantly, for many individuals with DSD conditions (including sex chromosomal DSD and conditions without genital ambiguity), gender assignment is not an issue, unless gender dysphoria is expressed later in life. While children with Klinefelter syndrome and (less severe) hypospadias without specific underlying genetic causes are generally assigned the male gender, children with CAIS, complete gonadal dysgenesis and individuals with 46,XX CAH are generally assigned as females. For conditions with partial virilisation (e.g. partial androgen insensitivity syndrome [PAIS] or partial gonadal dysgenesis) or more extensive genital ambiguity of other causes in individuals with 46,XY karyotype, the initial gender assignment can be either male or female. Similarly as in the attitudes towards gender-atypical behaviour, parental attitudes and sexism were shown to influence gender assignment in those with genital ambiguity (Joseph et al., 2017; Khorashad et al., 2016); parents favour male assignment in the context of the patriarchal societies they live in. Qualitative studies explored the experiences of parents with gender assignment and gendered upbringing of children with 46,XX CAH and observed that parents with virilised girls reported more fear of stigmatisation, complex surgical decisions and uncertainty pertaining to disclosing the condition, when compared with parents of children with 46,XX CAH reared as boys (Fleming et al., 2017). This finding could largely be attributed to the sex atypical bodies girls with 46,XX CAH may

have and pose parents for these specific difficulties. As a result, some families are advised to receive additional psychological counselling during childhood development. It is usually discouraged by both clinicians and most community stakeholders not to assign a gender to children and to raise children genderless (Lee et al., 2016). A fully genderless upbringing is generally considered practically impossible, as well as thought to complicate the processes of gender modelling and socialisation, although no studies on this topic have been performed.

11.4.3 Gender Dysphoria and Change

Some individuals may experience gender dysphoria and a subset of those may also change their gender socially, legally and/or medically. Although gender dysphoria and change are relatively infrequent in individuals with DSD conditions, it is more prevalent than in the general population (Furtado et al., 2012; Kreukels et al., 2018). Gender dysphoria is reported to be present in 8.5–20% of individuals with DSD conditions (lifetime prevalence varies per condition; Furtado et al., 2012), although reliable data are lacking given the heterogeneity in samples, definitions of gender dysphoria and measures used. In a recent large pan-European study surveying individuals across the DSD spectrum, the prevalence of gender dysphoria at follow-up in adulthood (mean age 32 years) was below 1% (measured by scores above 3SD on the Utrecht Gender Dysphoria Scale; Kreukels et al., 2018). In this study, gender variance (i.e. gender identification and/or behaviour other than male/female-typical societal norms) was seen in 3.6% (reported in all DSD groups, except women with Turner syndrome) and gender variant individuals scored poorer on psychological self-report outcomes such as higher gender dysphoria, lower self-esteem and higher levels of anxiety and depression, compared with gender-typical individuals. At follow-up in adulthood, around 5% of individuals with DSD conditions reported a gender change, ranging from 0% (sex chromosomal conditions) to 14% in 46,XX CAH and 16% in men with 46,XY DSD (Kreukels et al., 2018); of those, most gender changes took place before puberty (also observed by Jürgensen et al., 2010).

Gender dysphoria and cross-gender identification have been linked to specific clinical diagnoses as well as levels of virilisation. Highest numbers of gender dysphoria and change have been reported in 5α-reductase and 17β-hydroxylase deficiency, followed by PAIS and 46,XX CAH (Batista et al., 2018; Furtado et al., 2012). In girls with 46,XX CAH, androgen exposure is associated with more cross-gender identification, regardless of gender role behaviour, when compared with control girls (Pasterski et al., 2015). In the same line, women with 5α-reductase deficiency with the highest degree of virilisation at birth report the least gender conformity (based on satisfaction with gender identification) compared to their counterparts with lower virilisation (Nascimento et al., 2018). Moving away from the sex-binary, some individuals identify as gender variant or outside the binary: 1% of adults with DSD conditions reported to have an open, other or inter-gender

identity (Kreukels et al., 2018), while this may be an underestimation given the sampling and survey method. Qualitative studies further endorse the idea that many studies may have underestimated the levels of gender variance experiences within the DSD group. When speaking in-depth with this group, Brunner et al. (2016) found that although many individuals with CAIS usually live/identify as women, a substantial group (5 out of 11) did not feel typically female. This further puts the role of hormones into perspective; while testosterone exposure was observed to mediate gender-typical development, knowing to have chromosomes incongruent with the expressed gender, be infertile or have atypical physical characteristics may contribute to feelings of gender variance in individuals with DSD conditions. Furthermore, the concept of gender dysphoria may be less applicable in the presently more gender variant societies; although gender identity and (sex-specific) bodily characteristics may be incongruent, distress does not necessarily have to be present. It is important to differentiate clinical services: Those with varying identities and questions regarding self-understanding may benefit from supportive counselling, whereas those with gender-related distress and associated mental health issues may need more extensive psychological care. More research should be done to obtain a more differentiated non-normative view on experienced gender identity and expression in individuals with DSD conditions, using non-binary measures, and how these findings translate to affirmative healthcare across the lifespan.

11.5 Sexual Development in DSD

Sexuality, including adequate sexual function and good sexual well-being, is largely acknowledged as an important aspect of quality of life. In individuals with DSD conditions, sexuality may be influenced by sex-atypical physical appearance, sex hormone replacement therapy, past genital surgeries, as well as psychological issues such as doubts about identity, body image and self-esteem (Callens et al., 2020; Kreukels et al., 2019). Sexual development research in individuals with DSD conditions has focused largely on sexual orientation, sexual behaviour and sexual function (including sexuality-related anxieties) (Berenbaum & Meyer-Bahlburg, 2015; Cohen-Kettenis, 2010), whereas more data on sexual well-being and positive sexual traits have become available too (Dear et al., 2019; Schönbucher et al., 2012).

11.5.1 Sexual Orientation

Sexual orientation has been studied most in women with 46,XX CAH; the majority of women with CAH identifies as heterosexual, although same-sex attraction is relatively more frequent than in female controls (Cohen-Kettenis, 2010). Percentages of homosexual/bisexual women are reported in up to around 15% among women with 46,XX CAH, compared to <5% in control women (Gondim et al.,

2018; Jürgensen et al., 2013). Non-heterosexual orientation in women with 46,XX CAH is associated with more virilisation at birth (Gondim et al., 2018). Also, albeit studied in small samples, Frisen et al. (2009) also found evidence for differing likelihood of same-sex attraction over the different 46,XX CAH genetic mutations. Individuals with more "severe" genotypes reported more frequent non-heterosexual orientation, albeit individuals with milder CAH variants reported higher frequencies than reference values too.

In individuals with 46,XY DSD conditions, individuals without androgen effects (i.e. CAIS and complete gonadal dysgenesis) largely report heterosexual orientation (i.e. attraction to men) (Cohen-Kettenis, 2010), whereas up to half of the groups with DSD conditions with intermediate virilisation (between male-female-typical) reported non-heterosexual orientation (e.g. 5α-reductase and 17β-hydroxylase deficiency and PAIS; Batista et al., 2018; Schönbucher et al., 2010; Schönbucher et al., 2012). In a recent study, non-(exclusive) heterosexual orientation was reported across all DSD conditions (7.7–28.5%), including in individuals with sex chromosomal conditions; 21.5% in women with Turner syndrome and 17.5% in men with Klinefelter syndrome (Kreukels et al., 2019). Others have also observed that in women with 46,XY conditions with little androgen effects/exposure, sexual orientation is more variable than is usually presumed (Brunner et al., 2016). Altogether, whereas homosexual/bisexual orientations have mostly been observed in women with 46,XX CAH, non-exclusive heterosexual orientation is observed across the DSD spectrum, emphasising the need for an open non-normative approach by clinicians.

11.5.2 Sexual Behaviour and Function

Becoming sexually active is a part of entering adolescence. In adolescents with DSD conditions, sexual activity may be accompanied by hesitance, insecurities or even anxiety and avoidance (Cohen-Kettenis, 2010). A consistent finding in the literature is the phenomenon that individuals with DSD conditions have later romantic and sexual debuts, most likely as the result of postponing engaging in sexual encounters (Cohen-Kettenis, 2010; Sandberg et al., 2012). Also, a greater proportion of individuals of all DSD subgroups report not to be sexually active at all, when compared to control populations, although exact percentages vary (Callens et al., 2016; Kleinemeier et al., 2010; Schönbucher et al., 2010); among the DSD conditions, (adult) women with 46,XX CAH (46%; mean age 30) and Turner syndrome (53%; mean age 32) and men with a 46,XY DSD (59%; mean age 23) showed the highest percentage of sexual inactivity (Kreukels et al., 2019). Lower engagement was not only observed in sexual activity, but also in (later) first kiss and masturbation (Kleinemeier et al., 2010), and in lower general sexual interest (Schönbucher et al., 2010).

Sexual function may be impacted by both biological and psychosocial factors. Multiple studies have brought forward the substantial proportion of individuals with

DSD conditions having sexual dysfunction(s), both objectified through clinical levels of the Female Sexual Function Index (e.g. 66% in Callens et al., 2012, with poorest scores on the pain subscale) as well as on self-report incidences of sexual problems (e.g. an average number of 1.8 in Turner syndrome to 3.9 in 46,XY women) (Kreukels et al., 2019). In the latter study, both lack of sexual desire (mostly in non-virilised women with 46,XY), as well as excessive desire (mostly in Klinefelter syndrome), fear of sexual contact (mostly in all subgroups with 46,XY conditions), problems in reaching orgasm (more than 30% in women with 46,XX CAH, individuals with 46,XY DSD or Klinefelter syndrome) and pain (mostly in women with 46,XY) were reported by individuals. Sexual communication problems were observed as well (Schönbucher et al., 2010).

Several factors have been found to influence experienced sexual function, including genital appearance (Callens et al., 2016), hypogonadal hormone status (Vignozzi et al., 2010), decreased fertility (Cohen-Kettenis, 2010), prior genital surgery (Callens et al., 2016), body image, self-esteem and mental well-being (Kreukels et al., 2019; Weijenborg et al., 2019). On another note, surgery appears not to be the main determining factor. One study observed that a substantial share of women with DSD conditions were already sexually active prior to vaginal surgery (Dear et al., 2019). Also, other researchers found that sexual dysfunctions were prevalent in women with DSD conditions regardless of genital surgery (Callens et al., 2012). This has been confirmed in other studies finding that sexual function in individuals with DSD conditions is primarily determined by psychological factors, rather than biomedical factors (Ferlin et al., 2018).

11.5.3 Psychosexual Well-being

Over the course of time, the focus of sexuality research has somewhat shifted/broadened from sexual orientation and (dys)function to more positive aspects such as satisfaction and well-being. Satisfaction with sex life in individuals with 46,XY is around 50% (Schönbucher et al., 2010), which is impacted by sexual function and genital appearance, and is substantially lower than the 75% satisfaction rate reported in the general population (Dunn et al., 2000). Sexual satisfaction appears to be associated with the underlying DSD conditions (with women with Turner syndrome being least dissatisfied, when compared with the other DSD groups), sexual frequency (lower frequency and lower satisfaction were associated), not having a partner and higher levels of depressive symptoms (both negatively associated with sexual satisfaction) (Kreukels et al., 2019). Other factors that have been reported to be associated with sexual well-being and sexual quality of life in individuals with DSD conditions include having undergone genital surgery (Schönbucher et al., 2010, 2012), clinical diagnosis (Schönbucher et al., 2010, 2012), (genital) body image (van de Grift et al., 2018), sexual esteem (Dear et al., 2019; Schönbucher et al., 2012) and (self-)stigma (Meyer-Bahlburg et al., 2018).

Given the aforementioned long-term sexual issues and the extent to which psychosocial factors contribute, the consensus statement on treatment of individuals with DSD conditions states that psychosocial care by trained mental health professionals and a sexologist should be an integral part of care in order to support positive adaptation to having DSD conditions (Lee et al., 2016).

11.6 Conclusion: Sex and Gender as Continuum

Throughout history, individuals with DSD conditions have challenged the sex binary. While much of modern medicine has focused on supporting individuals with DSD conditions to comply with the sex binary (e.g. through psychological counselling or "normalising" genital surgeries), contemporary approaches increasingly view sex as a continuum with individuals with DSD conditions being somewhere on the scale between typical male and female (Ainsworth, 2015). Although parenting a child with sex ambiguity remains challenging, and there is little empirical evidence on how best to support families in a non-binary non-normative way, more societal and clinical openness towards less medicalised approaches to DSD has arisen. Similar developments are taking place for variation in gender identity and expression. Recent studies from Germany and Israel describing normative samples state that around 10–35% of individuals report (some) variance in their gender identity and/or expression (Becker et al., 2017; Joel et al., 2014). Possibly, this increasing gender diversity could pave the way for more societal accommodation towards sex variance as well.

Spotlight Feature: Testosterone, Science, and Sport

Eric Vilain[1,2] and Maria Jose Martinez-Patiño[3,4]
[1]Center for Genetic Medicine Research, Children's National Hospital, Washington, DC, USA
[2]Department of Genomics and Precision Medicine, George Washington University, Washington, DC, USA
[3]EpiDaPo (Epigenetics, Data, Politics), CNRS International Research Unit, Washington, DC, USA
[4]Faculty of Education and Sport Sciences, University of Vigo, Vigo, Spain
e-mail: evilain@gwu.edu; mjpatino@uvigo.es

Testosterone: 1, Women in Sport: 0

On May 1, 2019, the Court of Arbitration of Sports (CAS) handed down a political decision barring a number of women athletes from competing in the women category. When South African middle-distance runner Caster Semenya—a woman who won multiple Olympic medals and championships—tried to compete at the 2019 World Athletics Championships in Doha, Qatar, she was not allowed to participate with her fellow women because she refused to modify drastically her own physiology for no medical reason, but rather, to satisfy a policy from the International Association of Athletics Federations (IAAF), now World Athletics, based on the interpretation of data from studies of androgen levels in elite athletes which showed that women with free testosterone in the upper tertile (top third) performed better than women in the bottom tertile in a small number of events (Bermon & Garnier, 2017).

We know about sports authorities' policies on gender. We (a geneticist of sex development and a former athlete, now professor, prevented to compete because of her chromosomal constitution (Martínez-Patiño, 2005)) are both advisors to the International Olympic Committee (IOC) on questions of sex classifications in sports. The IOC is responsible for the organization of the Olympic Games while international sports federations (such as World Athletics) administer the rules and regulations of a sport. However, in order to become an Olympic sport, a sports federation must be recognized by the IOC, resulting in a high influence of the IOC on sports rules and regulations. We supported a compromise between a policy based on pure self-declaration of gender and a strict, genetically based definition of sex. We agreed with the use of a functional biological marker relevant to sport (Testosterone, or "T"), and the setting of the lower male-typical range of T (at the time considered to be about 10 nmol/L) as a threshold for allowing an athlete's participation in the female category for all events and regardless of their sex chromosomes. This guideline, adopted for the 2012 Games, was based on the perspective that T is a major factor in athletic performance and that a male-typical threshold would be a logical line of separation. Because the T threshold was high, it was inclusive of many athletes with a Difference of Sex Development (DSD). However, in 2016, Indian athlete Dutee Chand successfully challenged the guideline. In their ruling suspending the guidelines, the Court of Arbitration of Sports (CAS) explained that IAAF could not demonstrate that T accounts for the *entirety* of the 10–12% difference between male and female performance in athletics and requested IAAF to produce additional data to justify the guidelines. Two years later, IAAF produced

a new set of eligibility rules lowering the T limit to 5 nmol/L, applicable only to a small number of "restricted events," limited to distance running from 400 m to the mile. Yet, the major article on which this new policy is based (Bermon & Garnier, 2017) does not include the 1500 m nor the mile (both restricted), but includes hammer throw and pole vault, which were not restricted. In 2019, Caster Semenya challenged the new regulations, but this time, CAS upheld them.

There are two main issues with the new IAAF regulations and the CAS decision. First, rather than relying on scientific data, the guidelines are arbitrary. The basis for the IAAF rules is a single original article (Bermon & Garnier, 2017) that not only does not address the choice of a new T threshold level but has been heavily criticized by scientists due to methodological flaws (Pielke et al., 2018). Data allegedly included duplicated athletes (more than one track and field performance time per athlete), duplicated times (same time taken into account more than once for some athletes), and even phantom times (no athlete found with the reported time for the event). More importantly, there is no published evidence supporting if, as CAS claims, "female athletes with 46 XY DSD enjoy a significant performance advantage over other female athletes without such DSD." In addition, the choice of specific "restricted events" from 400 m to a mile is highly problematic, as there is little to no data relevant to 1500 m and the mile (a fact acknowledged by CAS, who still agreed to let IAAF include these two events as part of the guidelines). Also, the choice of restricted events may lead to the full absurdity of having the same athlete eligible as a woman for one event (e.g., 200 m) but not for another (e.g., 400 m). Finally, the rules apply to athletes with "sufficient androgen sensitivity for those levels of testosterone to have a material androgenising effect," yet there is no proposed accurate way to measure androgen sensitivity in the athletes affected by the policy. With so much at stake, a reasonable approach would be to resolve the scientific controversies first before relying entirely on questionable data to edict a rule. This would revert to the 2012 policy in which the testosterone threshold level was higher (10 nmol/L) and applied to all women in all disciplines, without discriminating against the biological cause of the androgen levels (Bermon & Garnier, 2017).

This brings us to the second, most disturbing consequence of the CAS ruling: the targeting of women with a Y chromosome. It took 3 decades (from 1968 to 1999) and multiple discriminatory rulings against women with a Y chromosome for sports authorities to remove sex chromosomes as the marker for eligibility in women's competition (Patiño et al., 2006). The regulations based on testosterone levels, introduced in 2012, were applied to all women regardless of their sex chromosome complement. Now the philosophy behind the policy is switching to accommodate the testosterone levels of most women with a common hyperandrogenic condition called Polycystic Ovary Syndrome (PCOS) who are all XX and for whom the upper limit is 4.8 nmol/L (99.99% one-sided confidence limit) (Handelsman et al., 2018; World Athletics, 2018). Interestingly, the rules read "These Regulations do not apply to any other conditions (including, without limitation, polycystic ovary syndrome), even if such conditions cause the individual to have blood testosterone levels above the normal female range." A woman with an XX karyotype and a PCOS condition resulting in a T level above 5 nmol/L (which has been reported) will be eligible while

a woman with an XY karyotype and the same T level will not, defying the logic of considering T as the major factor influencing athletic performance.

This new ruling throws us back to times when chromosomes would define who is a man and who is a woman for the purpose of sports, reminiscent of the exclusion from competitions of athletes such as one of us authors, Dr. Maria Patiño, based on sex chromosome constitution (Martínez-Patiño, 2005). This approach aligns with highly controversial attempts to redefine sex based only on the appearance of the genitals and, if disputed, on a genetic test (Green et al., 2018). Now that a growing number of countries (including top Olympic countries such as Germany and Australia) allow for non-binary gender on legal documents, the regulations appear out of step.

After decades of using scientific data to justify rules of eligibility for women in sports, with little to show in terms of improving fair participation in competitions, it is time for sports authorities to interpret cautiously the imperfect science of athletic performance and focus on the well-being and inclusion of an increasingly diverse population of athletes. In short, testosterone is being weaponized to achieve a policy result, rather than being considered with all its scientific complexity.

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