Are We Prepared to Abandon the Idea of Sex Binarism? A Biomedical Perspective

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Keywords

Disorders of sex development · Diversity · Gender · Social stereotypes

Introduction

Boy or girl? This is most probably the first question asked about a baby, when born until a few decades ago or, nowadays, at the time of pregnancy at which ultrasound imaging allows it. Indeed, the social categories “male” and “female” have been considered as indispensable and unchanging [1]. The “sex” of individuals is stated in all identity documents, starting from the birth certificate. However, important societal changes have occurred in recent years.

Sex and Gender

In the biomedical field – I will refer essentially to mammals and most often to humans – the word “sex” tends to be reserved to designate the biological aspects of an individual: the ovaries are female gonads, and the testes are male; oestrogens are predominantly female hormones and androgens, predominantly male. From a biological

standpoint, sex is determined by the presence of a Y chromosome, which triggers the differentiation of the gonadal primordium through the testicular pathway in early fetal life, finally resulting in the virilization of the internal and external genitalia. Two testicular hormones are the main responsible for fetal virilization: testosterone is androgenic steroid hormone that provokes the differentiation of the male internal ducts (epididymis, vas deferens, seminal vesicle) and, after transformation into the more potent androgen dihydrotestosterone, drives the differentiation of the prostate and the male urethra and external genitalia; anti-Müllerian hormone is a glycoprotein responsible for the regression of the Müllerian ducts, thus resulting in the absence of a uterus and Fallopian tubes in the male. In the absence of testicular hormones, genitalia undergo female differentiation [2, 3]. This genetic-gonadal-genital sex or “3G-sex” binary categorisation system [4] allows to classify more than 99% of individuals as either “male” (XY, testes, vasa deferentia, seminal vesicles, penis, scrotum) or “female” (XX, ovaries, fallopian tubes, uterus, vagina, clitoris, labia minora and majora). The basis of this powerful binary categorization relies on the facts that (i) there is a complete dimorphic presentation at the different levels of 3G-sex (i.e., 46,XY vs. 46,XX, testes vs. ovaries, vas deferens vs. uterus, scrotum vs. labia majora, etc.), and (ii) there is a high degree of consistency

between the different levels of 3G-sex for each one of the 2 categories (i.e., the “male” form at the genetic level highly likely associates with the “male” form at the gonadal and genital levels).

Instead, gender is a psychosocial concept: it is the self-perception of an individual (gender identity) or the perception the society has about someone (gender behaviour, expression, or role) [5]. According to the appearance, the way of dressing or behaving, a person can have a biological sex, e.g., female, and feel or be socially perceived of the opposite gender, i.e., male. A person is considered cisgender when identifying with the biological sex the person carries, and transgender when identifying with the opposite biological sex. Agender refers to a person who does not have a specific gender identity and bigender refers to a person who has two gender identities – which should not be confused with bisexuality, referring to the case of a person experiencing romantic or sexual attraction to two genders. According to, for instance, whether a person wears trousers and likes cars or wears skirts and likes dolls, the person may be perceived by others (“gender behaviour, expression or role”) as male or female or a mixture of both (“androgynous”). Furthermore, some persons may not identify with either gender or identify temporarily with one gender and temporarily with the other; this is referred to as gender fluidity (note that all these definitions are not universally accepted and that there are many other possibilities, see [6]). Independently of the gender identity or role, a person may feel affectively and sexually attracted to another of the opposite gender and is considered heterosexual, to another of the same gender and is considered homosexual (lesbian for females, gay for males), to both and is bisexual or to none and is asexual. The myriad of combinations of biological sex with gender identity, gender role, and sexual orientation give rise to a multitude of possibilities. Diversity in sexuality has traditionally been recognised by many Native Americans/First Nations peoples in North America, indigenous groups in South America, Polynesian societies in Hawaii and Tahiti and some social groups in India [7]. For instance, male-bodied individuals in a woman’s dress amongst the Sauk and Fox Nation in the Huron and Michigan lakes area have been depicted by European painters in the early 1800’s [8]; amongst the Mapuche living in Chilean and Argentine Patagonia, homosexual male shamans (“machi weye”) wearing female clothing were described in a Spanish chronicle of 1673 [9]; in native Hawaiian and Tahitian cultures, male-born Māhū (“in the middle”) have traditionally been third-gender individuals especially valued as teachers of chant

and hula dance and as keepers of cultural traditions [10]. Sexual diversity has received more widespread acceptance in Western societies during the last decades. This approach – which is not universally accepted [11] – distinguishes sex from gender, allowing for expressions of gender unanchored in bodily sex and displacing male – female duality as the basis of sexual relationships [12].

Sexual Dimorphism, Differences, and Fluidity

While the primordia of the gonads and the genitalia are identical in all early embryos of a given species, a clear sexual dimorphism arises during fetal development. For instance, in the human embryo until the 6th week of gestation, the gonadal ridges are sexually undifferentiated, there are 2 sets of internal genital ducts – the Wolffian ducts and the Müllerian ducts – and the primordia of the external genitalia show no differences between the XX and the XY embryos. But, between the 7th and the 13th weeks of gestation, the gonads differentiate into ovaries or testes, the Wolffian ducts give rise to the epididymides, the vasa deferentia and the seminal vesicles in the XY fetus, whereas the Müllerian ducts originate the Fallopian tubes and the uterus in the XX fetus, and the external genitalia evolve either to the penis and scrotum or to the clitoris and the labia [3]. In other words, there is a clear sexual dimorphism in the development of the reproductive organs [4]. There are sexual differences in other organs, e.g., the brain [13, 14], the liver, or skeletal muscles [13], but these differences may not allow to distinguish two separate categories, i.e., there is no strict sexual dimorphism [4]. This means that for a certain variable or characteristic, while there is a biggest difference between categories than within categories (e.g., males are taller than females and have bigger brain size [15] and lower superoxide dismutase activity in the liver [13]), it is not possible to predict to which category (“sex”) the individual belongs just by analysing only that variable or characteristic (stature, brain volume, superoxide dismutase activity in the liver). The same concept of difference, rather than dimorphism, applies to gender.

Another concept to consider is that of fluidity or plasticity, referring to the capacity of a characteristic to vary with time. The concept of gender fluid, i.e., a person who does not identify with gender binarism and moves across gender stereotypes, has gained acknowledgement in recent years. Plasticity also applies to anatomic characteristics, e.g., the mammary gland shows minor development in the male exposed to low oestrogen levels but may dif-

ferentiate female-like when chronically exposed to high oestrogen levels. There are, however, sex features that once fixed cannot vary to adopt the characteristics of the other sex, e.g., once the labioscrotal folds differentiate to form the scrotum by the effect of androgens by the 13th week of intrauterine life, they cannot transdifferentiate to labia majora by withdrawing androgen action.

Congenital Disorders of Sex Development and Their Management

The lack of coincidence between the sex chromosomes, the gonads, and/or the genitalia in an individual is referred to as a disorder of sex development (DSD), a term coined by consensus in 2005 to replace the nomenclature previously used and perceived as pejorative by patients [16]. In the past, the terms “intersex,” “hermaphroditism,” and “pseudohermaphroditism” had been used to refer to individuals presenting with ambiguous external genitalia that cannot be classified as male or female. In the concept of DSD, conditions not previously identified as “intersex,” “hermaphroditism,” or “pseudohermaphroditism” were included (Table 1). Here, I will refer to DSD classically requiring medical attention because of the existence of ambiguous genitalia or a discordance between apparently normal external genitalia and the individual’s karyotype (46,XX with male genitalia or 46,XY with female genitalia) [3]. Klinefelter syndrome (47,XXY with male genitalia) and Turner syndrome (45,X with female genitalia) prompt diagnostic approaches that differ substantially from the other forms of DSD, and will not be addressed here.

The birth of a child with ambiguous genitalia prompts a long-term management strategy involving a multidisciplinary professional team working with the family. Remarkable progress could be observed in recent years in the diagnosis and treatment of patients with DSD, as well as in the understanding of psychosocial issues and the acknowledgement and acceptance of the place of patient advocacy [17, 18]. One particular consideration is the importance of the patient’s participation in decision-making. This is especially challenging when considering congenital conditions that may require treatment before the patient develops the capacity to give an opinion.

Of the many issues in the management of patients with DSD, particular attention have received medical decisions that result in irreversible situations. Those addressing life-threatening conditions do not raise controversy. Conversely, unresolved debates exist around irreversible

genital surgery without the patient’s informed consent [19]. For instance, patients with ovotesticular DSD (known as “hermaphroditism” before the 2005 Consensus [16]) carry both ovarian and testicular tissue; when sex assignment is made, the gonadal moiety that does not coincide with the assigned sex is excised to avoid the effect of undesired hormone secretion at the age of puberty (e.g., androgens that could virilise a patient raised as girl, or oestrogens that could provoke breast development in a patient raised as boy). This irreversible surgery, which used to be performed early in infancy decades ago, is now usually delayed until just before the age of puberty, thus allowing the participation of the child in decision-making. Patient’s participation in decision-making, whenever possible, is particularly important in the case of individuals with DSD, since some of these disorders show a higher risk of gender dysphoria, i.e., the sense of discomfort or distress that may be felt by persons whose gender identity differs from the sex assigned, resulting in gender change [20–22].

Another controversial situation is, for instance, the surgical correction of hypospadias, i.e., the presence of the urethral opening in the ventral side of the penis as a consequence of insufficient androgen action during the first trimester of fetal life. Hypospadias repair is not vital and, unless technical advantages of early surgery can be demonstrated, the main reason for its implementation seems to be psychosocial. A child with hypospadias is unable to urinate standing up, and seated urination is a characteristic associated with the female gender. Although hypospadias is the commonest malformation of the penis, little information is available to the general population, leading to psychological distress in patients and their parents [23]. Support to families in parenting children with genital ambiguity in order to facilitate psychological adjustment could be efficacious to avoid unnecessary early surgeries.

Is the Society Prepared to Abandon the Idea of Sex Binarism to Deal with Medical Conditions Such as DSD?

Driven by advocacy groups, the society has incorporated the concepts of sexual diversity. Legislations exist now in many countries that simplify gender change, as well as marriage of and parenting by same-gender couples, or even relieve the need to define sex or gender in identity documents such as the birth certificate or the passport. From a healthcare perspective, the issues to be

Table 1. Classification of DSD

DSD type	Pathogenic classification	Aetiology	Examples	Gonads	Internal genitalia	External genitalia	Nomenclature before 2005*
46,XY DSD	Malformative DSD	Defective morphogenesis of the genital primordia	Cloacal exstrophy Isolated hypospadias	Testes	Male or dysmorphic	Male or dysmorphic	Non-classified
	Disorders of gonadal differentiation	Complete (pure) gonadal dysgenesis	Swyer syndrome	Streak	Absence of male ducts Uterus and fallopian tubes	Female	Complete sex reversal
	Partial gonadal dysgenesis		Campomelic dysplasia	Dysgenetic testes	Hypoplastic/dysmorphic male ducts Hypoplastic/dysmorphic uterus and fallopian tubes	Ambiguous	Male pseudohermaphroditism
	Disorders of testicular hormone production or action	Disorders of androgens production	Leydig cell aplasia/ hypoplasia 17 β -HSD deficiency 5 α -reductase deficiency	Testes	Hypoplastic/dysmorphic/absent male ducts No uterus and fallopian tubes	Ambiguous/female	Male pseudohermaphroditism
	Disorders of androgen action		AIS	Testes	Hypoplastic/dysmorphic/absent male ducts No uterus and fallopian tubes	Ambiguous/female	Male pseudohermaphroditism (testicular feminisation)
46,XX DSD	Disorders of AMH synthesis or action		PMDS	Testes	Male ducts Uterus and fallopian tubes	Male, cryptorchidism	Internal male pseudohermaphroditism
	Malformative DSD	Defective morphogenesis of the genital primordia	Cloacal exstrophy MRKH syndrome	Ovaries	Female/dysmorphic	Female/dysmorphic	Non-classified
	Disorders of gonadal differentiation	Ovotesticular DSD	<i>NR5A1</i> variants	Ovotestes/ovaries + testes	Hypoplastic/dysmorphic male ducts Hypoplastic/dysmorphic uterus and fallopian tubes	Ambiguous	Herma-phroditism
	Testicular DSD		<i>SRY</i> translocation	Testes	Male	Male	XX male
	Ovarian dysgenesis		<i>BMP15</i> variants	Streak/dysgenetic ovaries	Hypoplastic uterus and fallopian tubes	Female	Ovarian failure (not included as intersex)
Sex chromo-some DSD	Disorders of steroid hormone production	Androgen excess	CAH Aromatase deficiency	Ovaries	Hypoplastic uterus and fallopian tubes	Ambiguous/male	Female pseudohermaphroditism
	Disorders of gonadal differentiation	Ovotesticular DSD	46,XX/46,XY and variants	Ovotestes/ovaries + testes	Hypoplastic/dysmorphic male ducts Hypoplastic/dysmorphic uterus and fallopian tubes	Ambiguous	Herma-phroditism
	Asymmetric gonadal differentiation		45,X/46,XY and variants	Testis + streak	Asymmetric (male on the testis side, ambiguous/female on the streak side)	Ambiguous	Mixed gonadal dysgenesis
	Turner syndrome		45,X and variants	Streak	Hypoplastic uterus and fallopian tubes	Female	Turner syndrome
	Klinefelter syndrome		47,XXY and variants	Testes	Male	Male	Klinefelter syndrome
	Triple X syndrome		47,XXX and variants	Ovaries	Female	Female	Triple X syndrome

HSD, hydroxysteroid dehydrogenase; PMDS, Persistent Müllerian duct syndrome; AIS, androgen insensitivity syndrome; CAH, congenital adrenal hyperplasia; AMH, anti-Müllerian hormone; MRKH, Mayer-Rokitansky-Küster-Hauser. *Date when the nomenclature from the Chicago consensus was established [16].

considered to decide on the best treatment strategy in patients with DSD include the anatomical appearance of the gonads and genitalia, the pathophysiology of the condition, psychosocial issues and sociocultural influences, as well as ethical, legal and human rights implications [17]. Although the application of a gender perspective has been most helpful in the progress of healthcare management of patients with DSD, it seems that a perception of urgency to introduce changes has prompted some flaws.

On the one hand, healthcare of patients with DSD and that of individuals with gender issues (e.g., transgender) are being mixed up. Even if some treatment options may be shared, such as hormone therapy [17, 18, 24], differences associated with gender diversity should not be confused with disorders in fetal sex development. Here, careful wording is important: we have seen that there is a wide range of possibilities in gender perception and choice, with no dimorphism, and not resulting from a health disorder. These are therefore “differences.” Conversely, the biological process of fetal sex differentiation shows a clear dimorphism, and intersex conditions are discernible health conditions, with an underlying pathophysiology identified in the majority of them (disorders of gonadal development, defective sex-hormone synthesis or action [3, 17, 18]) and even a genetic aetiology diagnosed in a considerable proportion [25]. DSD are therefore “disorders.” It is obvious that a disorder is a difference; yet not all differences are disorders. Differences in sex development or similar terminology not deemed offensive by patients and their families could be preferred in a social context when talking with patients and their families or when addressing social media. However, “disorder” or another acceptable term with the same degree of precision could be preferred within the professional setting especially now, in the age of precision medicine aiming at personalised management of health issues [26]. To avoid distrust of clinicians by patients, resulting from the use of terminology considered offensive, there is a need for greater dialogue on the right terminology. At present, the situation is becoming confusing, especially when using “differences in sex development” to refer to DSD and keeping as subclasses “disorders of gonadal differentiation,” “disorders of hormone synthesis or action,” etc. (Table 1).

On the other hand, in terms of involving the patients and their families in decision-making, we seem to be putting the horse before the cart. Legislative bodies in some countries have recently banned irreversible genital surgery performed without the patient’s informed consent [17]. Is a boy with hypospadias prepared to seated urina-

tion until the age he will be able to give his opinion about surgical treatment, without suffering from social distress? There is no evidence of the potential effects of delaying surgeries performed as part of standard care at present [19]. Under the current social perception, despite the recent societal incorporation of the concept of sexual diversity, gender stereotypes are deeply anchored: gender is considered a primary feature in person perception, even when this binary categorisation is not relevant to the situation and has no informational benefits [1]. Men continue to be overrepresented in traditionally male engagement, such as breadwinning, and underrepresented in traditionally female care-oriented engagement, such as household tasks and childcare [27], and society seems to have a long way to go before gender stereotype neutrality will be achieved according to contemporary change rates (e.g., as long as 134 years for implicit male-career/female-family stereotypes [28]). Finding ways to raise resilient children with ambiguous genitalia could be far more efficacious and less harmful than banning early genital surgery in the management of patients with DSD. Indeed, parents seek solutions from medical attention when they face the hitherto socially stressful situation of not knowing whether their child is a girl or a boy. Once parents and their children with hypospadias will perceive no anxiety about seated urination, early surgery will not need to be banned in order to be dumped.

Final Remarks

Confusion is not a good advisor. There are features that are sexually dimorphic and others that are not. Not all differences are disorders, and those prompting medical attention are most probably disorders. The technically precise language to be used in the professional setting should certainly differ from the empathic language to be used with patients, their families, and lay public. Changes in healthcare should accompany societal changes rather than anticipate them.

Conflict of Interest Statement

The author is an established researcher with the Argentine National Research Council (CONICET, Argentina). He has received honoraria from CONICET for technology services using the anti-Müllerian hormone ELISA kit until 2020, as well as lecture honoraria from Novo Nordisk and Sandoz, and travel grants from Biosidus, Merck, Novo Nordisk, Pfizer, and Sandoz.

Funding Sources

No specific funding was received for the preparation of this manuscript.

Author Contributions

The author conceived the manuscript outline, performed the bibliographic search, and wrote the manuscript.

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