J Endocrinol Invest
DOI 10.1007/s40618-016-0482-0

REVIEW

Gender identity, gender assignment and reassignment in individuals with disorders of sex development: a major of dilemma

A. D. Fisher[1] · J. Ristori[1] · E. Fanni[1] · G. Castellini[1,2] · G. Forti[3] · M. Maggi[1]

Received: 20 October 2015 / Accepted: 4 May 2016
© Italian Society of Endocrinology (SIE) 2016

Abstract
Introduction Disorders of Sex Development (DSD) are a wide range of congenital conditions characterized by an incongruence of components involved in sexual differentiation, including gender psychosexual development. The management of such disorders is complex, and one of the most crucial decision is represented by gender assignment. In fact, the primary goal in DSD is to have a gender assignment consistent with the underlying gender identity in order to prevent the distress related to a forthcoming Gender Dysphoria. Historically, gender assignment was based essentially on surgical outcomes, assuming the neutrality of gender identity at birth. This policy has been challenged in the past decade refocusing on the importance of prenatal and postnatal hormonal and genetic influences on psychosexual development.
Aims (1) to update the main psychological and medical issues that surround DSD, in particular regarding gender identity and gender assignment; (2) to report specific clinical recommendations according to the different diagnosis.
Methods A systematic search of published evidence was performed using Medline (from 1972 to March 2016). Review of the relevant literature and recommendations was based on authors' expertise.
Results A review of gender identity and assignment in DSD is provided as well as clinical recommendations for the management of individuals with DSD.
Conclusions Given the complexity of this management, DSD individuals and their families need to be supported by a specialized multidisciplinary team, which has been universally recognized as the best practice for intersexual conditions. In case of juvenile GD in DSD, the prescription of gonadotropin-releasing hormone analogues, following the World Professional Association for Transgender Health and the Endocrine Society guidelines, should be considered. It should always be taken into account that every DSD person is unique and has to be treated with individualized care. In this perspective, international registries are crucial to improve the understanding of these challenging conditions and clinical practice, in providing a better prediction of gender identity.

Keywords Disorders of Sex Development · Gender Dysphoria · Gender identity · Gender assignment · Gender reassignment

✉ M. Maggi
m.maggi@dfc.unifi.it

[1] Sexual Medicine and Andrology Unit, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy

[2] Psychiatric Unit, Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

[3] Endocrine Unit, "Center for Research, Transfer and High Education on Chronic, Inflammatory, Degenerative and Neoplastic Disorders for the Development of Novel Therapies" (DENOThe), Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Careggi Hospital, Florence, Italy

Introduction

Sexual differentiation

The normal pattern of human sexual development occurs in a highly regulated and dynamic process, dictated by intricate genetic activity, and executed by endocrine mediators in the form of steroid and peptide hormones [1, 2]. According to

Published online: 10 June 2016

the pioneering Jost's paradigm, the first sexual development step is constituted by the establishment of the chromosomal sex (i.e., the presence of a Y or X chromosome), at the time of fertilization [3]. Then, the chromosomal sex influences the determination of the gonadal sex, in differentiating the bipotential gonadal ridge into either a testes or an ovary. The presence and expression of the testes-determining gene SRY, located on the distal part of the short arm of the Y chromosome (Y_p), determines the gonadal sex of an embryo by directing the development of the bipotential embryonic gonad into testes, with formation of Sertoli and Leydig cells [4]. The differentiation of male testes leads to the secretion of specific hormones responsible for translating gonadal sex into male internal and external genitalia (sex phenotype) [1]. In particular, the anti-mullerian hormone (AMH), produced by Sertoli cells, causes the regression of the Mullerian ducts and prevents the development of the uterus, fallopian tubes, and the distal portion of the vagina [5, 6]. Meanwhile, testosterone secretion from Leydig cells promotes the Wollfian duct differentiation into vasa deferentia, epididymis, and seminal vesicles [5, 6]. Testosterone is then converted by the tissue-specific isoenzymes, 5-alpha-reductase type 1 and type 2, into dihydrotestosterone (DHT), which is responsible for the masculinization of the external genitalia, including phallic enlargement, closure of the urethral folds, and development of the prostate and scrotum [7, 8]. Without the influence of the sex-determining gene located on the distal part of the short arm of the Y chromosome (Y_p), the development of the embryonic gonad will be driven along the female pathway [5, 9]. The Müllerian ducts develop without any apparent hormonal input into the uterus, fallopian tubes, and the distal portion of the vagina, whereas the Wolffian ducts regress and disappear in the absence of androgenic stimulation [10]. In addition, the genital tubercle develops as a clitoris, the urethral folds form the labia minora, and the labioscrotal swellings give rise to the labia majora.

To the aforementioned model, Money et al. [11] added the concept of psychosexual development. As demonstrated by animal experiments, the process of sexual differentiation is not completed with the formation of genitalia, but also the brain, as the substrate of sexual and non-sexual behavior, undergoes sexual differentiation consistent with the other characteristics of sex [12]. This paradigm suggests that androgens directly (or via the local conversion into estradiol) organize the brain in early development, and pubertal steroids further activate and reorganize the already organized brain, resulting in the expression of masculine behaviors [13–19]. The two crucial periods in human development when testosterone levels are known to be higher in male than in female individuals are mid-pregnancy and the first 3 months after birth [20, 21]. These two peaks of testosterone, together with functional changes in steroid receptors, are thought to fix (and "organize") the structures and circuits in the brain for the rest of a person's life. The rising testosterone levels during puberty activate and reorganize circuits that were built during development [14–16, 21, 22]. Therefore, psychosexual development is a complex and long-lasting process influenced by multiple factors, including brain structure, prenatal and postnatal hormonal and genetic influences, postnatal environmental and psychosocial experiences, and social and familiar circumstances [23–25], and is traditionally broken down into three domains: gender identity, gender role behavior, and sexual orientation [26, 27]. Gender identity refers to a fundamental sense of belonging and self-identification to one gender and to the extent to which a person experiences being like others of one's gender: male, female, or an alternative gender [28]. The term gender role describes the behaviors, attitudes, and personality traits that a society, in a given culture and historical period, designates as masculine or feminine, that is, more "appropriate" for, or typical of, the male or female social role [28]. Sexual orientation is defined by a person's responsiveness to sexual stimuli. The most salient dimension of sexual orientation is the sex of the person to whom one is sexually attracted. This stimulus class is how one defines a person's sexual orientation as heterosexual, bisexual, or homosexual [28]. Therefore, human sexual differentiation is a multistep, sequential, interrelated process in which genetic information is translated into the phenotype of a person who subsequently establishes a male or female identity and an awareness of sexual orientation [29–32].

On the basis of phenotypic sex, at birth, the legal gender is assigned, with the expectation that the social environment will support the formation of a corresponding social gender role for the child and that child will later develop gender-related behavior and a gender identity accordingly [33].

Any hindrance occurring during this complex process of sexual differentiation could lead to a misalignment between chromosomal, gonadal, and phenotypic sex, classically defined as Disorders of Sex Development (DSD) [34]. As brain sexual dimorphic differentiation is an integrating part of sexual differentiation, it should be considered that also the three components of psychosexual development—gender identity, gender role, and sexual orientation—may not always be concordant and aligned in individuals with DSD [35]. In fact, as sexual differentiation of the genitals takes places much earlier in development (i.e., in the first 2 months of pregnancy) than sexual differentiation of the brain (the second half of pregnancy), these two processes may be influenced independently. This means that in the event of ambiguous genitals at birth, the degree of masculinization of the genitals may not always reflect the degree of masculinization of the brain [36].

Interestingly, recent studies suggest that Gender Dysphoria (GD) could hypothetically be considered as a DSD limited to the central nervous system, without the involvement

of the reproductive tract [25, 33]. GD, according to DSM-5 criteria, is a condition characterized by a marked incongruence between one's experienced/expressed gender and the assigned one, associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning [37]. The assumption that GD could be considered a DSD is based on the demonstration in male-to-female (MtF) and female-to-male (FtM) transsexuals of a sex reversal in terms of volume and cell number of sex-dimorphic brain nuclei, such as the central portion of the bed nucleus of the striaterminalis (BNSTc) [38–40], the gray matter in the right putamen [41], and the interstitial nuclei 3 and 4 of the anterior hypothalamus (INHAH3 and INAH4) [42]. These findings have been further enhanced by the demonstration of gender-atypical brain activation patterns in processing steroid-based odors and erotic stimuli [43, 44]. In addition, a recent study found that FtM GD individuals show stronger more female-typical otoacustic emissions compared to control boys, suggesting that boys with GD might have been exposed to relatively lower amounts of androgens during early development [45]. In line with these studies, it has also been reported that MtF individuals have female-typical facial preferences in terms of sexual attraction [46]. It has also been postulated that there may be genetically based systemic sex hormone abnormalities that do no cause abnormalities of the reproductive anatomy, but nevertheless influence brain and behavior [33]. Some authors, for example, reported an increased number of trinucleotide CAG repeats in the androgen receptor gene in MtF transsexuals (generally linked to impairment of androgen action) [47]; an increased prevalence of CYP17 gene polymorphisms in FtM transsexualism [48], and of significant combined partial effects of three polymorphisms in MtF transsexualism (CAG repeats in the AR gene, CA repeats in the estrogen receptor beta-gene, and tetranucleotide repeats in the aromatase gene) [49].

Therefore, in a wider and more current perspective, DSD could be defined as all the conditions in which the chromosomal, gonadal, phenotypical or psychological (or rather gender identity) sex are incongruent [50].

Moreover, the overlap existing between DSD and GD is linked to the possibility in both conditions of discomfort or distress caused by a discrepancy between gender identity and gender assigned at birth [51, 52]. Furthermore, in both groups, such distress could lead to a possible gender reassignment request. In fact, in non-intersex persons, gender identity issues develop, even though all biological sex indicators are differentiated uniformly in the direction of one sex or of the other [53]. These indicators include sex chromosomes, sex-determining genes, the gonads, the systemic sex hormone milieu during fetal development, puberty, and adulthood, and the secondary sex characteristics [53]. Conversely, in intersex conditions, the misalignment concerns also the biological sex indicators. This concept has been emphasized in DSM-5 in which GD diagnosis includes both conditions, with and without DSD [37].

Finally, a theoretical relationship between GD subsequent to DSD and sexual orientation may be of interest. In fact, both gender identity and sexual orientation seem to be determined during early development, under the influence of a genetic background and factors involved in the interactions between sex hormones and the developing brain [35, 40]. However, it should be considered that, while GD in individuals with DSD may have an impact on the gender assignment and reassignment choice, this is not the case for sexual orientation. In fact, the distress and/or suffering related to a non-heterosexual orientation seems to be more the consequence of internalized homonegativity, defined as the negative attitudes toward homosexuality by gay and lesbian persons who reflect negative social beliefs [54].

Therefore, sexual orientation as well as gender-atypical behavior do not affect the decision-making process in DSD gender assignment. This may explain the fact that studies addressing systematically the relationship between gender-atypical behavior and sexual orientation in DSD are missing.

Genetic aspects involved in DSD

In case of DSD, a molecular diagnosis is made in only around 20 % of cases (excluding those due to a steroidogenic block [55]). Several new genes have been identified associated with human errors of primary sex determination [56, 57]. Approximately 15 % of 46,XY gonadal dysgenesis carries mutations in SRY, the majority of which localized within the HMG domain [56, 57]. Beyond SRY, additional sex-determining genes and transcriptional factors, such as SOX9, NR5A1, GATA4, DAX1, and DHH, induce a further maturation of the testes [56]. SOX9 plays an essential role in both the specification and differentiation of mesenchymal cells toward the chondrogenic lineage, as well as establishing Sertoli cell identity in the developing testis immediately following the expression of SRY [56]. Accordingly, recent studies have focused on SOX9 potential regulatory role in DSD development. Mutations involving NR5A1 are associated in humans to a wide range of genital anomalies, including gonadal dysgenesis with a male-to-female sex reversal, and adrenal insufficiency [58]. GATA4, interacting with several proteins, such as NR5A1, regulates the expression of genes crucial for testis determination and differentiation [58]. Accordingly, different mutation in GATA4 has been reported associated with errors of testis determination [56]. A role of Desert Hedgehod (DHH) in establishing the fetal Leydig cell lineage is supported by the gonadal dysgenesis observed in patients carrying homozygous mutations, possible due an impairment of Sertoli cell–Leydig cell interaction [56].

Regarding female sexual differentiation, different signaling molecules have been shown to be necessary for normal ovarian development, such as R-spondin 1 (RSPO1) and WNT4 [59, 60]. RSPO1 mutations have been reported in syndromic cases of XX testicular DSD, while mutations of WNT4 are associated with various degrees of virilization (including androgen excess and abnormal development of Mullerian ducts) in 46,XX women.

Aims

The aims of the present review were as follows:

1. to update the main psychological and medical issues that surround DSD, in particular regarding gender identity and gender assignment;
2. to report specific clinical recommendations according to the different diagnoses, when possible.

Methods

A systematic search of published evidence was performed including the following words ("sex development" [All fields] OR "intersex" [All fields] OR "ambiguous genitalia" [All fields]) AND "gender identity" [MeSH] AND ("humans" [MeSH Terms] AND English [lang]). The search accrued data from January 1, 1955 (the year that John Money published his well-known paper on hermaphroditism, currently referred to as DSD [11]) up to March 2016. Studies focusing on GD without DSD, genetics aspects of DSD, and sexual satisfaction were not considered for this review. The identification of relevant studies was performed independently by three of the authors (A.D.F., M.M., J. R.), and conflicts resolved by the third investigator (G.F.).

Gender assignment in DSD

One of the most difficult issues in a child with DSD diagnosis, particularly in case of ambiguous genitalia, is the assignment to the more appropriate gender, and, from a parent's perspective, the gender of rearing [61, 62]. According to many authors, the primary goal in DSD was for gender identity to be consistent with the gender assigned and to avoid a gender assignment that would increase the risk of GD [25, 35]. In fact, although there is no clear manifestation of GD, it has been reported that both individuals with 46,XX (27.3 %) and 46,XY (45.5 %) may show a discomfort with their gender identity [63]. For many years, according to the "optimal gender policy" developed by Money [11, 64], it was believed that gender identity should have been concordant with assigned sex, assuring that the child is raised unambiguously and that appropriate surgical "corrections" and hormone therapies are instituted in line with the gender chosen. This assumption was based on the belief of the neutrality of gender identity at birth, which develops its characterization on the basis of postnatal social and environment influences [64]. Based on this policy, Money suggested assigning a gender to a child with DSD as soon as possible and to adjust his/her genitalia surgically in early childhood. Then, in his opinion, the gender of rearing will later influence the gender identity and gender role of the patient. In this perspective, recommendations for gender assignment of children with ambiguous genitalia have been historically guided by the phenotypic appearance of the genitalia, on the basis of which sex would offer the child the best opportunity for success particularly in aesthetical, fertility, and sexual terms. Accordingly, most surgeons have recommended early surgery, in order to "normalize" the genitalia [62]. For example, a 46,XY subject judged as having an inadequate penis was assigned female, whereas a virilized 46,XX patient with ovaries and a uterus was assigned female, independently of the degree of external genitalia virilization [35]. In addition, parents were counseled to not disclose the intersex state of the child and often shrouded these conditions in great secrecy [61].

This theory, assuming psychosexual neutrality at birth, has been challenged in the past decade by refocusing on the potential importance of prenatal (e.g., endocrine) and genetic influences on psychosexual development [5, 18]. In addition, the recent criticism for the management of DSD in the past is the result of adults who experienced interventions too early and have reported GD and uneasiness related to the gender assigned. Moreover, many other individuals report their previous management as an abuse of their human rights [65].

Theoretically, assignment should be made as quickly as a thorough diagnostic evaluation permits. Because DSD is an uncommon phenomenon, there has been limited data concerning the eventual outcomes regarding gender identity, gender role identification, or sexual orientation, and in many of these conditions, information about long-term gender development is unfortunately not syndrome-specific [66–71]. The effect of hormonal imprinting on gender development may be elucidated through existing animal models and also the observations of human case studies in DSD patients [61]. Influencing factors include diagnosis, genital appearance, therapeutic options, sexual and fertility potential, cultural practices and pressures, and parental view. Individual DSD outcome data regarding gender identity, quality of life (QoL), avoidance of unnecessary surgery, hormone replacement, and fertility preservation must be considered in deciding gender assignment [72–74]. Sexual potential, one the most difficult aspect to predict,

is also a key factor to be considered for male or female assignment [75]. Particularly, penis length and its potential to develop during puberty into a sexually functional penis are crucial aspects to take into account if male assignment is considered. The majority of patients with 5-alpha-reductase-2 deficiency with a male assignment report satisfactory sexual function as long as they present an adult penis length at least 6 cm [76]. Despite the majority of individuals with 5-alpha-reductase-2 deficiency present a male gender identity, it should be considered that those assigned female have been reported with satisfactory sexual activity [77]. Among patients with partial androgen insensitivity syndrome (PAIS), male gender assignment should be considered when there is a satisfactory response to testosterone therapy in terms of phallic growth, as well as an established causative genetic variant [75]. A female assignment is suggested if testosterone treatment is without effects [75]. Regarding persons with 17-beta-hydroxysteroid dehydrogenase type 3 (17-beta-HSD-3) deficiency, sexual dissatisfaction has been reported in both male and female gender assignments [75].

Available studies suggest that, in women with congenital adrenal hyperplasia (CAH), interpersonal dynamics and the individual's abilities to cope with different sexual and relational situations have more impact in sexual satisfaction than genital anatomy [75, 78].

Also fertility potentials should be considered in the decision-making process for gender assignment, particularly before performing an early gonadectomy. For example, in 5-alpha-reductase-2 and in PAIS patients, sperm retrieval and ICSI may be considered [75, 79].

In summary, if a specific diagnosis can be made, recommendations for gender assignment can be based upon outcome data, when available for the specific DSD diagnosed, which are more specifically addressed below in Table 1 [61, 80]. The Chicago Consensus statement did not include specific diagnoses, but some consensus participants have provided more specific recommendations described here [80]. However, long-term outcomes are needed to establish standardized practice guidelines for decision making [81]. Moreover, timing of genital surgery should be also taken into account. Families should be always made aware of and counseled about the pros and cons of early and late assignment [62]. In addition, even when recommendations for gender assignment are clear, arguments exist on whether surgery can be delayed until the individual can participate in the decision and provide consent [62]. In line, some countries, as Germany, have recently introduced the possibility to legally choose "male," "female," or "x" in the public register to ease the pressure of an early assignment for newborns DSD.

In any case, it should be taken into account that every DSD subject is unique and has to be treated with individualized care, preferably with a multidisciplinary approach [2, 82, 83] always in the best interest of the child.

Table 1 Recommendations for gender assignment by DSD diagnosis (Houk and Lee [35], Yang et al. [61] modified)

Diagnosis	Recommended sex assignment
46,XX DSD	
CAH	Female
46,XY DSD	
5-alpha-reductase-2 deficiency	Male or female
17-beta hydroxydehydrogenasi 3 deficiency	Male or female
Complete gonadal dysgenesis	Female
Complete androgen insensitivity syndrome	Female
Partial androgen insensitivity	Male or female
Androgen biosynthetic defects	Male or female
Incomplete gonadal dysgenesis	Male or female
Micropenis	Male
Cloacal exstrophy	Male or female
Hypospadias	Male
Ovotesticular DSD	Male or female

DSD disorders of sex development

Gender reassignment

It should be considered that a small minority of DSDs feels the need to change gender later in life, and therefore, the assigned gender should not be considered immutable [84]. However, it is usually recommended for gender reassignment to be always initiated by the patient and must be approached very cautiously [72]. Because childhood gender dissatisfaction may remit, young individuals have to be carefully evaluated by skilled specialists in order to identify the multifaceted determinants of gender identity, as well as biological and social factors (i.e., family functioning and support) [72, 85]. In fact, it should be considered that, in a considerable percentage of individuals, childhood GD does not persist throughout adulthood, possibly because in the development phase gender identity is still fluctuating [86–88]. Furthermore, addressing a possible comorbid psychiatric disorder is also essential for better hormonal treatment compliance and for building a stable gender identity [66]. Finally, sexual and fertility potentials need to be addressed with the patient. A similar exhaustive psychosocial and medical assessment can guide team decisions about gender reassignment, timing of surgery, and sex hormone replacement [72]. In particular—when gonads are still present and possibly functioning—if eligibility criteria are fulfilled (see Table 2) [51, 89, 90], puberty may be

Table 2 Eligibility criteria for GnRHa and cross-sex hormone treatment

Adolescents are eligible for GnRHa treatment if they
1. Meet the DSM-5 criteria for GD
2. Have experienced puberty at least up to Tanner stage 2
3. Have an increase in GD at the arrival of (early) pubertal changes
4. Do not suffer from psychiatric comorbidities that interfere with the diagnostic work-up or treatment
5. Have adequate psychological and social support during treatment, and
6. Demonstrate knowledge and understanding of the expected outcomes, risks and benefits of therapy
7. The parents consent to the treatment and give adequate psychological and social support during treatment
Adolescents are eligible for cross-sex hormone treatment if they
1. Meet the criteria for GnRHa analogues
2. Are 16 yrs or older
3. The parents consent to the treatment and give adequate support during

GnRHa gonadotropin-releasing hormone analogues, *GD* gender dysphoria

temporary suspended by using gonadotropin-releasing hormone analogues (GnRHa). This treatment leads to a gradual regression of sex characteristic development, aiding in prolonging the diagnostic phase, whereas the body remains in a neutral early pubertal state. Such option could allow both the adolescent and the clinician to achieve greater gender clarity and awareness [91]. This option may be particularly relevant in case of GD in DSD conditions where no clear gender identity outcome can be predicted (see Table 1). In line with the Standards of Care of the World Professional Association for Transgender Health [89], it is recommended starting GnRHa when adolescents have experienced puberty to at least Tanner stage 2, because of the important diagnostic value of the negative emotional effects related to the first pubertal changes [51, 89, 90]. In particular conditions (such as in case of a gender assignment at birth different from the recommended one), an earlier treatment with GnRHa may be also considered. This could be, for example, the case of a late diagnosis of a 46,XY DSD in which a male assignment is usually recommended (such as 5-alpha-reductase-2 deficiency). In such condition, if a female assignment at birth is performed and no GD is experienced thereafter (because of a female gender identity), a puberty suppression could be considered, avoiding the (male) puberty progression. The latter, in fact, could be perceived by the adolescent as a natural disaster, devastating his/her body and (gendered) integrity [92]. We have also to consider that in that case, differently from GD without DSD, puberty is characterized by physical modifications, possibly inducing a switch in the phenotypic sex.

In case of GD persistence and if eligibility criteria are met (see Table 2), puberty induction in accordance with the adolescent gender identity should be considered [51, 89, 90].

MHP role with patients with DSD

The issues that surround DSDs are multidimensional and require both an individualized and multidisciplinary approach to provide effective diagnosis, treatment, and support [55, 80]. The ultimate aim of treatment and care for patients with DSD are the physical, psychological, and sexual well-being within a "patient-centered" view and a continuous teamwork [93]. Considering the difference in physical appearance and the variation in developmental history, the basic processes of successful social and emotional development, as well as self-concept, may be more challenging for children and adolescents with DSD than for their peers [94]. Therefore, MHPs may play an important role in the different phases of the management of DSD. Children born with DSD and their families may have different needs, and therefore, the connection with MHPs as early as possible may ensure that proper help can be available when and if psychological needs do arise. Regarding the diagnostic phase, MHPs play a role in the assessment and management of various mental health needs of the child and the family. For example, a psychologist could provide support and assist families who may be having difficulty coping with the diagnosis of genital ambiguity in their child [95] or with the uncertainty about psychosocial and psychosexual outcomes of the child development. This implies that parents should be supported in the heavy responsibility perceived in decision making, as for example gender assignment, options, and timing for early medical and surgical interventions [96]. In some cases, identifying and clinically managing DSDs can begin even before a child is born; such moments can be perceived as extremely stressful as these can often lead to irreversible (and irremediable) outcomes in terms of QoL, psychological and medical well-being, and sexual function and satisfaction. Therefore, MHPs should always provide information about

the pros and cons of any elective interventions [96, 97] and inform about the results of medical examinations and about the available knowledge on gender development in similar situations [96]. Also, MHP may evaluate the parents or care givers in terms of their education, cognitive capacity, coping skills, as relevant to their ability to understand the DSD and to nurture a child with a DSD [93]. Possibly, the responsibility for treatment decision and adherence to medical treatment can shift to the child, when mature enough to become personally engaged in his/her care. Also assessment of parent/child relationship and facilitation of healthy parent/child relationship should always be performed and investigated [93]. Parents may need help in practical aspects related to the DSD management, as the balance between secrecy and sharing the medical conditions in the social context (who should be told, how and when should the information been given) [50]. In fact, the experience of DSD could be stigmatizing for the parents leading them to avoid family, friends, and social support. Moreover, parental emotional support should be offered for the possible responsibility and guilty feelings that parents may experience about their child with a DSD.

Studies on the psychiatric characteristics of children with DSD are scarce [82]. If psychiatric comorbidity is present, it is important to treat the patients with any diagnosis of a psychiatric disorder for better treatment compliance; furthermore, being without severe psychiatric complaints is also essential for building a stable gender identity [82]. In this regard, it has been reported that gender dissatisfaction (unhappiness with assigned sex) is more frequent in individuals with DSD than in the general population [82]. Also the child's cognitive functioning should be defined in order to assess the child's ability to participate in the decision-making process, to explore options. Active participation of the child underlines the autonomy and personhood of the patient [93], improving self-efficacy and self-esteem.

Puberty can be a challenging period, and some adolescents with DSD may develop anxieties. For example, they may postpone initiating intimate relationships because of insecurities and fear of rejection [96]. During adolescence, while sexual maturation occurs, it is important to promote a healthy self-image, as well as addressing sexuality and fertility issues within an age-appropriate education. Sexual problems indeed occur more often in DSD than non-DSD groups [72, 87, 88, 97]. In some cases, MHPs may work on the patient's feelings regarding sexual orientation, if issues of internalized homonegativity or struggles with dealing with stigma arise. In adolescence, questions may emerge or re-emerge about gender identity, gender reassignment, and surgical intervention (e.g., some may need to know why they have to dilate the vagina or have to make decisions about genital surgery) [96]. The sharing of more detailed information with the child is an imperative during this stage [96].

MHPs, together with the family, play also a role in the disclosure of medical and surgical history that should occur in an age-appropriate manner and according to the developmental level of the child [97].

Peer support represents another useful form of care for patient with and their family, in both formal (in a clinical setting, e.g., support groups) and informal (through personal connections, e.g., Internet groups) settings. In fact, meeting others who share the similar challenges has been consistently identified by adults and families affected by DSD as one of the most therapeutic experiences [50].

Finally, MHPs play an important role in facilitating the group process within the team and between the team and the family [96].

QoL of patients affected by DSD and their parents

One of the main aims of care for patients with DSD should be a good QoL that may be defined by a feeling of general health and well-being, being able to work, to have an active social life, and to form long-lasting, close relationships [98]. DSDs include different conditions that are characterized by some common aspects, but also by specific difficulties in each diagnostic group and at certain times: for example, at the initial diagnosis, during the developmental stage, at symptom control, during fertility treatment, or at the beginning and end of an important relationship [75]. Therefore, people with DSD may be affected at different levels in their QoL areas during lifetime. Currently, studies on long-term QoL are scarce [98]. In general, follow-up studies have indicated dissatisfaction with overall sex life and sexual function [3–5, 98], as well as with binary gender [99], negative body image [100], social isolation [101], and experiencing normalizing surgery as dilemmatic [102]. Also, children are described by decreased health-related QoL, whereas parents by lower levels of emotional well-being and lower QoL mental health scores than among community samples [103]. In line with the psychological aspects related to DSD described previously, early and constant contact with a MHP should be available for children/adolescent with DSD and their families in order to have a good QoL by promoting competence and experienced efficacy in both parents and children with DSD.

Hormone replacement therapy

Hormonal treatment is influenced by the specific DSD involved and by social factors, such as gender of rearing and gender identity [91].

DSD with male gender assignment and identity

In infants born with micropenis, 25 mg intramuscular (IM) testosterone enanthate every month for 3 months is recommended to induce penile growth. In children with micropenis at preschool age, a further short course of 25–50 mg IM testosterone enanthate for 3 months can be used [91]. This is particularly the case when children experience social anxiety or difficulties in urinating while standing, or if there are concerns regarding adequate penile length for penetrative sexual intercourse in adulthood [104].

Induction of male puberty in individuals with known DSD should be started from the age of 12 years through increasing dose of intramuscular, oral, or topical testosterone. Adverse effects of androgen pubertal induction include erythrocytosis, weight gain, and irreversible development of male secondary sex characteristics, which may be distressing in case of GD. Intramuscular testosterone esters can be started at a dose of 50 mg monthly, increasing by 50-mg intervals every 6–12 months to a dose of 250 mg monthly, at which point a long-acting adult testosterone formulation can be commenced (testosterone undecanoate 1000 mg every 12 weeks, [51, 91]). Otherwise, oral testosterone undecanoate 40 mg daily can be given with the evening meal and gradually titrated upward every 6 months to an adult dose of 160–240 mg per day, or to other testosterone formulations [51, 91]. Topical testosterone gel (available as 1 or 2 % testosterone strength) can be started with one-third of the daily adult dose for the first year and gradually increased by one-third daily every year to the adult daily dose by the third year [51].

In the case of patients with PAIS reared as males, in order to overcoming the androgen resistance, supra-physiological doses of testosterone (up to five times of the typical dose for age) can be used to induce virilization, decrease gynecomastia, and improve body mass density [105]. Aromatase inhibitor can be added to prevent the development of gynecomastia.

High dose of testosterone has been used in the past also in 5-alpha-reductase deficiency to optimize available enzyme function. Alternative, topical treatment with 2.5 % of dihydrotestosterone gel has been reported to increase successfully virilization in affected persons [91].

DSD with female gender assignment and identity

In girls with DSD and absence of endogenous estrogen production (i.e., for gonadal digenesis or gonadectomy), pubertal induction can be started since the age of 11 years, using estrogens at gradually increasing doses [51, 91]. In a setting of short stature, it is preferred to start estrogen from 12 years, to maximize the pubertal growth spurt. Natural estrogens, such as oral 17-beta-estradiol, are preferable to synthetic estrogens. Oral 17-beta-estradiol can be administered with a starting dose of 0.25 mg per day, increasing the dose every 6 months to an adult dose of 2 mg per day [91, 106]. The initial dose of transdermal 17-beta-estradiol is 6.2 mcg per 24 h (one-quarter of a 25 mcg/24-h matrix patch), increasing gradually to an adult dose of 100 mcg per 24 h. In the presence of a uterus, when the adult dose of estrogen is attained (or earlier if menarche occurs), progesterone must be added (e.g., medroxyprogesterone acetate 10 mg daily for the last 7 days of the menstrual cycle, [91]). In case of complete androgen insensitivity syndrome (CAIS) or PAIS, if gonadectomy is delayed after puberty, or event not performed, circulating oestradiol levels are enough to induce spontaneous development of female secondary sexual characteristics (including breasts, [105]). In the case of gonadectomy, supplementation of estrogens may be required in these patients in order to maintain serum oestradiol in the 300–400 pmol/l range [91, 105]. In patients who undergo gonadectomy before puberty, estrogens should be started at a low dose and up-titrated based on pubertal progression of bone age [105].

Specific clinical aspect according to different DSD diagnoses

46,XX DSD

Androgen excess in congenital adrenal hyperplasia (CAH) Of all 46,XX patients seen in clinical practice, CAH accounts for a vast majority. Inactivation or loss-of-function mutations in five genes critical to steroid biosynthesis are implicated in CAH (CYP21, CYP11B1, CYP17, HSD3B2, and StAR) [57, 107]. While all are characterized by impaired cortisol secretion, only CYP21 and CYP11B1 deficiencies are associated with a masculinizing disorder (and HSD3B2 to a lesser extent) in 46,XX individuals [1]. In fact, as one of the several endocrine consequences, 46,XX fetuses with these enzymatic deficiencies are exposed to unusually high levels of androgens during fetal development, which variably masculinize the genitalia and presumably also the brain and later behavior [50, 108, 109]. Defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol (CYP21 deficiency) accounts for more than 90 % of cases of CAH [110]. Psychosocial assessments have demonstrated that CAH women, when compared to controls, report more cross-gender typical role behavior and patterns during childhood [25, 63, 111, 112], with a preference for typically male toys [24, 111–116] and playmates [25, 114]. Moreover, it has been reported that they are less interested in maternal rehearsal play, feminine makeup, and accessories [115, 117, 118]. Few were comfortable with their sense of femininity during childhood [119]. When gender-related behavior assessment in adult women with CAH was performed as a function of

disease severity, it was observed that women with the non-classical or late-onset CAH showed few signs of gender shifts, the simple-virilizing women were intermediate, and the salt-wasting variants were the most severely affected [111]. Furthermore, a recent study has reported that gender identity, measured as a continuous variable, may correlate in 46,XX CAH with indicators of androgen exposure [120]. In addition, some studies reported a delay of sexual experiences, a reduced interest in sexual activities, lower maternalism, and a higher prevalence of bi- or homosexual orientation in women with CAH compared to the general female population [24, 25, 121–127]. Moreover, it has been observed that girls with CAH who show the greatest alterations in childhood play behavior may be the most likely to develop a bisexual or homosexual orientation as adults [122] and that rates of bisexual and homosexual orientation were found to be correlated with the degree of prenatal androgenization [109] as well with genotype severity [128].

However, when GD was considered, only a few cases have been described, with some changes from female-to-male gender, as reported by some authors [74, 123, 130–132]. In fact, even if there is a strong evidence (40.9 %) of behaviors considered more typical of male gender identity [63], the majority (95 %) of 46,XX patients with CAH raised as females develop a female gender identity later on [24]. Although this rate far exceeds GD in the general population, the absolute proportion is quite low [129, 133], and it cannot be predicted from genital virilization [22, 23, 128, 134]. It could be concluded on the basis of these findings that, as female gender identity is the most common outcome despite markedly masculinized gender-related behavior, patients diagnosed in the neonatal period, particularly with lower degrees of virilization (Prader 3 or less), should be raised as female [35, 95, 135]; those with delayed diagnosis may present more difficulties and may need to be evaluated carefully by a multidisciplinary team [61]. It should be considered in fact that cases of successful male assignment have been reported in 46,XX CAH individuals with late diagnosis and virilization resulting from hormonal imbalance [136, 137]. On this regard, Houk and Lee recently proposed consideration of male assignment for those with fully developed male genitalia when the parent's input is supportive [35]. In summary, a psychological counselling focused on gender identity and GD in CAH children and adolescents and in their families is recommended [95]. In addition, counselling should include also QoL issues, considering the poorer health-related QoL recently observed in these patients [95, 138, 139].

46,XY, DSD with typical female external genitalia at birth

Complete gonadal dysgenesia (Swyer syndrome) In 46,XY complete gonadal dysgenesia, no testicular development occurs and therefore patients present a complete lack of androgenization of the external genitalia and normal Müllerian structures, due to the absence of gonadal steroid and AMH production [95]. Some authors [140] suggest that subjects affected by Swyer syndrome, [5], have to be reared as female on the basis of following considerations:

1. Typical female psychosexual development is reported in this syndrome [141].
2. Pregnancy can be successfully carried out with egg donation by affected individuals reared as female [141–146].
3. Reconstructive surgery is not required for the external genitalia to be consistent with the female gender.
4. Hormone replacement therapy is needed at puberty irrespective of the gender of rearing due to the high risk in these cases of developing germ-cell tumors from the dysgenetic gonads [141, 143, 147, 148].

CAIS In XY individuals with CAIS, the external genitalia appear to be completely female at birth. However, due to the effect of the AMH secreted by the testes, inducing a regression of the Mullerian ducts, the internal genitalia are lacking [149]. Classically, patients present in adolescence with primary amenorrhea and absence of post-pubertal pubic and axillary hair, but can also be discovered in infancy with inguinal or labial swelling containing testis [95, 105]. Although estimations of the risk of developing gonadal malignancies vary, overall the risk before puberty is low in CAIS patients [105, 150, 151]. In addition, no relationship exists between the timing of performing a gonadectomy and bone mineral density. On these bases, it has been suggested that gonadectomy in CAIS may safely be delayed until after puberty [105], monitoring retained testes for the development of malignancy [152].

Regarding gender assignment, it has been suggested [95, 140] that subjects with a CAIS should be reared as female because:

1. In accordance with the presumed absent androgenization of the brain, CAIS subjects have a well-documented female-typical core gender identity, gender role behavior and sexual orientation toward males, and they do not appear to suffer from GD [25, 67, 153–156]. These data were confirmed by Mazur which reported in a review of the literature, among 157 subjects with CAIS assigned and raised as females, no cases of gender reassignment to male gender [149].
2. No surgery is needed for the external genitalia to be consistent with female gender [140].
3. Although hormone replacement treatment (with estrogens) is needed at the time of gonadectomy [105],

androgen resistance makes testosterone replacement untenable [147, 148].

However, two cases with some degree of GD have recently been reported [157, 158]. If in the first case the social and family pressures may have hypothetically contributed to the male gender assignment request [157], this was not the case of the second [158]. The latter had a strong and persistent GD leading to a complete male gender reassignment involving mastectomy and phalloplastic procedures [158]. According to the authors, the development of male gender identity in a phenotypic female patient, with a complete lack of a functioning androgen receptor, questions the role of the androgen receptor pathway in the development of male gender identity [158]. However, based on the convincing literature, and with the report of only few cases with GD, rearing subjects with CAIS as a female sex must remains a standard procedure.

5-alpha-reductase-2 deficiency Most newborns with 5-alpha-reductase-2 deficiency (the enzyme converting testosterone into dihydrotestosterone) have female external genitalia at birth, although few infants may present with ambiguous genitalia. Testes are usually undescended, the Wolffian ducts are stabilized to form epididymides, vas deferens, seminal vesicles, and ejaculatory ducts, and there is a blind vaginal pouch [1]. Most affected infants are assigned a female sex and raised as girls. Profound virilization occurs at puberty in the form of deepening of the voice, substantial growth of the phallus, rugation, and hyperpigmentation of the scrotum, as well as increased muscle mass. A gender role change from female to male during adolescence and adulthood is reported in 56–63 % of subjects [77]. Several factors may determine whether these subjects (as well as those with 17-beta-hydroxysteroid dehydrogenase type 3 deficiency, described below), raised as females, make a switch after puberty. A possible biological factor is represented by the severity of the deficiency in enzyme production, causing a variable exposition of the brain to androgens. However, the duration and extent of prenatal brain exposure to androgens is difficult to determine retrospectively at birth or later, and, unfortunately, no data are available on the relationship between the developing of a male gender identity and circulating androgens before, during, and after the gender role change. Moreover, cultural or other environmental pressures (such as family) have been mentioned has potential influencing factors. Furthermore, the genital appearance (male, female, or ambiguous) may influence the self-body image and therefore the gender identity. In summary, it has been postulated that the pubertal changes which occur in these subjects' bodies, in association with a masculine appearance in childhood and with masculine behavior (hypothetically caused by prenatal exposure to androgens), could reinforce an already existing gender discomfort [77]. On the basis of the reported high percentage of subjects requesting female-to-male gender reassignment after puberty, together with fertility potential [77, 159], a male gender assignment is normally recommended in these 46,XY DSD, despite the female-appearing external genitalia. In addition, it should be considered that in this syndrome, genital tissue is responsive to androgens, even if undermasculinized genitalia are unlikely to ever appear completely male-typical, despite medical and/or surgical treatment. Moreover, hormonal replacement is not necessary at puberty for subjects reared as male if the testes are not removed [140].

17-beta-HSD-3 deficiency

17-beta-HSD-3 deficiency results in impaired testicular conversion of Delta4-Androstenedione into testosterone [160]. Affected subjects commonly present a female appearance of the external genitalia at birth. Hence, female gender is generally assigned, and subjects are reared accordingly [161]. In subjects reared as females, if diagnosis has not been established before puberty and gonads are nor removed surgically, virilization occurs at puberty with development of male body habitus, male muscle mass, abundant body hair and beard, and deepening of the voice; enlargement of cricoid cartilage may be present. The clitoris enlarges, but it remains undersized compared to a penis. Testicular volume also increases and may reach the range of normal adult males. Gynecomastia does not usually occur, but has been reported in some patients [161]. A recent literature review reported that female-to-male gender role change occurs frequently (39–64 %) but not invariably, usually in late adolescence or early adulthood [77, 159–162]. As in 5-alpha-reductase deficiency, in 17-beta-HSD-3 deficiency, there is not to date a clear relationship between the severity of the enzymatic defect and gender identity and why changes in gender role occur in some patients but not in others [77, 162–167]. Moreover, it has been suggested that unidentified pre- and postnatal factors, a better knowledge of the natural history of the disorder in some areas, and sociocultural issues may participate, all together, in influencing gender identity and role [77, 161, 163]. In fact, biological factors aside, socialization and learning, have been shown to contribute significantly to gender identity and role [168]. Up to now, data supporting a male gender assignment in these subjects are not as strong as for 5-alpha-reductase deficiency. Moreover, it should be taken into account that an intermediate risk for germ-cell tumors exists for 17-beta-HSD-3 deficiency, and there are no reports of fertility thus far [140]. In particular, regarding the latter, it is unknown whether early testosterone therapy

and orchidopexy would result in a more favorable outcome [168]. Consequently, female gender assignment may be appropriate in some situations; regular testicular evaluation is required for those reared male who have not had their testes removed [147].

46,XY DSD with ambiguous external genitalia at birth

PAIS Despite normal androgen production, presentation of external genitalia in PAIS is highly variable and can range from a penis with perineoscrotal hypospadias, with or without cryptorchidism, to a micropenis, with or without hypoplasticlabioscrotal swellings, which may or may not be completely fused to form a scrotum [169]. Infants with PAIS are assigned to either the male or female gender, depending to some extent on the degree of hypomasculinization. Virilization at puberty is also variably incomplete [149]. Gender identity shows considerably greater fluidity among persons born with PAIS [96, 170]. In fact, gender is not fully defined by genotype or external genitalia, but is a complex phenomenon, involving biological and social factors [105]. Therefore, surgical and medical treatment can assign phenotypic sex, but not gender identity [105]. For example, on the basis of the Mazur review of literature, among 99 subjects diagnosed with PAIS, nine (both male and female initial sex assignments) changed gender during their lifetime [149]. In addition, GD without a complete gender change was also reported [171]. Interestingly, gender change has not been shown to be correlated with a specific androgen receptor gene defect. As the evidence available up to now does not provide a clear guideline on gender assignment, it should be concluded that gender assignment in newborns with PAIS remains challenging, but gender identity is usually in line with the gender of rearing. When possible, choices regarding nonessential and irreversible interventions should be delayed until the patient is old enough to take part in the decision-making process [105].

Isolated micropenis

Studies on subjects with micropenis demonstrated an inarguable establishment of male role by all patients, as well as the establishment of a successful sexual relationship [104, 149, 172]. In fact, it should be taken into account that testosterone therapy in micropenis caused by fetal testosterone deficiency results in a functionally adequate penis, even if penile length usually remains significantly shorter than the reference values for young adults [104, 173–175]. Available data suggest that there is no clinical [104], physiologic [176], or psychological [177, 178] basis for considering gender reversal in infants with micropenis and they should therefore be raised as males.

Cloacal exstrophy

46,XY subjects with cloacal exstrophy have been raised as female in the past, but recent studies suggest a variable outcome in terms of gender identity, as more than 60 % of subjects assigned female presented female-to-male gender change [179, 180]. On this basis, recent attitudes have changed among clinicians more often favoring male gender assignment in these subjects [180, 181].

Isolated hypospadias

Several factors related to hypospadias could expose the subject to an increased risk of psychosexual maladjustment: the stress related to a praecox genital surgery, the possible poor aesthetic and functional results of surgery procedures, and finally the abnormal prenatal androgen exposure and/or androgen receptor defects to which they have been possibly subject. It has been observed that a more pronounced masculine gender role behavior was predicted by a younger age at final surgery [182]. Vice versa, the number of surgeries has been found to be positively correlated with increased gender-atypical behavior [183].

Sex chromosome DSD

47,XXY Klinefelter syndrome and variants Men with Klinefelter syndrome, which is one of the most common forms of sex chromosome aneuploidy, usually report a male gender identity. However, a recent Belgian study described a significantly higher prevalence of Klinefelter syndrome among male-to-female GD [184] than expected, based on the population data [185]. In addition, a recent study showed the presence of higher dysphoric symptoms in Klinefelter persons compared to a group of healthy controls [186]. However, levels of GD observed were not at critical threshold to suggest a GD diagnosis and should be better considered in light of the dimensional construct of GD. Moreover, moderator analyses showed that gender dysphoric symptoms observed in Klinefelter population might be an epiphenomenon of the autistic traits [187].

However, it should be recognized that GD in Klinefelter syndrome has not been systematically studied in large samples, and it is possible that not all karyotype variations have been reported by other gender teams, specifically in relation to the finding of Klinefelter syndrome [184].

Mixed gonadal dysgenesis In individuals with mixed gonadal dysgenesis, marked differences in gonadal development and histology can be seen between the right and the left sides or even within a single gonad. Genital phenotypes could range from normal female external genitalia or mild clitoromegaly through all stages of ambiguous genitalia, to

hypospadias or to normal penis. Prenatal androgen exposure, internal ductal anatomy, gonadal function and, after puberty, phallic development, and gonadal location have to be considered when sex rearing must be decided [187].

Ovotesticular DSD Also known as "true hermaphroditism," ovotesticular DSD is characterized by the presence of both ovarian and testicular tissues in either the same or opposite gonad and by genital ducts which usually differentiate following the homolateral gonad. Most patients have ambiguous genitalia at birth or significant hypospadias. At the time of puberty, breast development, menses, and progressive androgenization could occur depending on the significance of ovarian and testicular tissue. The management varies on the basis of the age of diagnosis and anatomical differentiation. Either male or female assignment may be appropriate when the diagnosis is made at a young age and gender identity has not yet become defined. The decision on sex of rearing in ovotesticular DSD should consider the potential for fertility based on gonadal differentiation and genital development and assuming the genitalia are, or can be made, consistent with the chosen sex [107, 187].

Summary

The suggested strategy for gender assignment of a newborn with genital ambiguity should not be based only on the appearance of the genitalia at birth, as the degree of genitalia virilization does not necessary correlate with the degree of brain masculinization. In fact, there are temporal trends in gender assignment that are independent of this external appearance. The results from a recent analysis in Europe (I-DSD registry) [188] clearly reveal that the practice of assigning female sex in newborns with 46,XY DSD seems to be decreasing. The change in practice was not due to a higher degree of masculinization of the cases raised as boys. This practice could have been influenced by reports on adequate long-term outcome in men with 46,XY DSD and conditions such as micropenis and an improved surgical outcome of penile reconstruction or neophallus construction [174]. It is likely that this practice has also been influenced by those cases of XY DSD who were raised as girls and who developed GD, although other similar cases in which GD was not encountered have received less attention [179]. In summary, the multidisciplinary DSD team needs to carefully weigh and balance the genital appearance, the clinical options (also in terms of fertility), the cultural pressures as well as the parental view and support [95]. Moreover, when a specific diagnosis can be made, recommendations for gender assignment can be based upon outcome data, when available for the specific DSD diagnosed. Regular psychological support and gender counselling should be available to the child and the family as part of a multidisciplinary service to DSD in order to ensure psychological and social well-being throughout different developmental stages. Furthermore, a psychological evaluation is recommended in case of distress or discomfort related to gender-atypical behaviors experienced by the child or by his/her family. In particular, this should be performed by a MHP skilled in GD in children and adolescents to assess the child's gender identity, the presence of GD, and psychosocial functioning. In case of GD in DSD conditions where no clear gender identity outcome can be predicted, the prescription of GnRHa, following the WPATH and the Endocrine Society guidelines [88, 89], should also be considered. Such option could allow the child and family to gain time to clarify gender issues and reassignment decision making. Also, in the case of a gender assignment at birth different from the recommended one, an early psychological evaluation performed by a MHP as well as the prescription of GnRHa should be considered, in some cases also before puberty onset. A complete social transition to the opposite gender is recommended in case of strong and persistent GD and desire to live fully in the opposite gender role and/or in case of an early onset of cross-gender behaviors [88].

In conclusion, it should be taken into account that every DSD subject is unique and has to be treated with individualized care. Researches for further understanding of specific outcomes are needed. In this perspective, international registries (e.g., I-DSD Registry, DSD-Life, DSD-net, and DSD-TRN, [96]) are crucial to improve the understanding of these challenging conditions and clinical practice, in providing a better prediction of gender identity and common clinical procedures [96, 188–190].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Kim SS, Kolon TF (2009) Hormonal abnormalities leading to disorders of sexual development. Expert Rev Endocrinol Metab 4:161–172
2. Hiort O, Birinbaun W, Marshall L, Wunsch L, Werner R, Schroder T, Dohnert U, Hoterhus PM (2014) Management of disorders of sex development. Nat Rev Endocrinol 10:520–529
3. Jost A (1972) A new look at the mechanism controlling sex differentiation in mammals. Johns Hopkins Med J 130:38–53

4. Koopman P, Gubbay J, Vivian N, Goodfellow P, Lovell-Badge R (1991) Male development of chromosomally female mice transgenic for SRY. Nature 351:117–121
5. Achermann JC, Hughes IA (2008) Disorders of sex development. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR (eds) Williams textbook of endocrinology, 11th edn. Elsevier Saunders, Philadelphia
6. Cameron F, Smith C (2004) Embryology of the female genital tract. In: Balen A, Creighton S, Davies MC, MacDougall J, Stanhope R (eds) Paediatric and adolescent gynaecology: a multidisciplinary approach. Cambridge University Press, Cambridge, pp 3–8
7. Migeon CJ, Wisniewski AB (2003) Human sex differentiation and its abnormalities. Best Pract Res Clin Obstet Gynaecol 17:1–18
8. Siiteri PK, Wilson JD (1974) Testosterone formation and metabolism during male sexual differentiation in the human embryo. J Clin Endocrinol Metab 38:113–125
9. Sinclair AH, Berta P, Palmer MS, Hawkins JR, Griffiths BL, Smith MJ, Foster JW, Frischauf AM, Lovell-Badge R, Goodfellow PN (1990) A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. Nature 346:240–244
10. Pasterski V (2008) Disorders of sex development and atypical sex differentiation. In: Rowland DL, Incrocci L (eds) Handbook of sexual and gender identity disorders. Wiley, Hoboken, pp 354–374
11. Money J, Hampson JG, Hampson JL (1955) An examination of some basic sexual concepts: the evidence of human hermaphroditism. Bull Johns Hopkins Hosp 97:301–319
12. Gooren L (2010) The endocrinology of sexual behavior and gender identity. In: Jameson L, de Groot LJ (eds) Endocrinology—adult and pediatric, 6th edn. Elsevier Saunders, Philadelphia
13. Arnold AP (2009) The organizational–activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. Horm Behav 55:570–578
14. Bramen JE, Hranilovich JA, Dahl RE, Chen J, Rosso C, Forbes EE, Dinov ID, Worthman CM, Sowell ER (2012) Sex matters during adolescence: testosterone-related cortical thickness maturation differs between boys and girls. PLoS ONE 7:e33850
15. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL (1999) Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 2:861–863
16. Lenroot RK, Gogtay N, Greenstein DK, Molloy Wells E, Wallace GL, Clasen LS, Blumenthal JD, Lerch J, Zejdenbos AP, Evans AC, Thomphons PM, Giedd JN (2007) Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 36:1065–1073
17. McCarthy MM, Arnold AP (2011) Reframing sexual differentiation of the brain. Nat Neurosci 14:677–683
18. Phoenix CH, Goy RW, Gerall AA, Young WC (1959) Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65:369–382
19. Meyer-Bahlburg HFL, Baratz Dalke K, Berenbaum SA, Cohen-Kettenis PT, Hines M, Schober JM (2016) Gender assignment, reassignment and outcome in disorders of sex development: update of the 2005 consensus conference. Horm Res Paediatr 85:112–118
20. Quigley CA (2002) Editorial: the postnatal gonadotropin and sex steroid surge-insights from the androgen insensitivity syndrome. J Clin Endocrinol Metab 87:8–24
21. Swaab DF (2007) Sexual differentiation of the brain and behavior. Best Pract Res Clin Endocrinol Metab 21:431–444
22. Swaab DF (2004) The human hypothalamus. Basic and clinical aspects. Part II: neuropathology of the hypothalamus and adjacent brain structures. In: Aminoff MJ, Boller F, Swaab DF (eds) Handbook of clinical neurology. Elsevier, Amsterdam
23. Cohen-Brendahan CC, Van de Beek C, Berendbaum SA (2005) Prenatal sex hormone effects on child and adult sex-typed behavior: methods and findings. Neurosci Biobehav Rev 29:353–384
24. Jürgensen M, Kleinemeier E, Lux A, Steensma TD, Cohen-Kettenis PT, Hiort O, Thyen U, Köhler B, DSD Network Working Group (2012) Psychosexual development in adolescents and adults with disorders of sex development: results from the German Clinical Evaluation Study. J Sex Med 10:2703–2714
25. Meyer-Bahlburg HF (2013) Sex steroids and variants of gender identity. Endocrinol Metab Clin North Am 42:435–452
26. Meyer-Bahlburg HF, Dolezal C, Baker SW, Carlson AD, Obeid JS, New MI (2004) Prenatal androgenization affects gender-related behavior but not gender identity in 5–12 years old girls with congenital adrenal hyperplasia. Arch Sex Behav 33:97–104
27. Money J (1994) The concept of gender identity disorder in childhood and adolescence after 39 years. J Sex Marital Ther 20:163–177
28. Zucker KJ (2002) Intersexuality and gender identity differentiation. J Pediatr Adolesc Gynecol 15:3–13
29. Byne W (2006) Developmental endocrine influences on gender identity: implications for management of disorders of sex development. Mt Sinai J Med 73:950–959
30. Gooren L (1990) The endocrinology of transsexualism: a review and commentary. Psychoneuroendocrinology 5:3–14
31. Gooren L (2006) The biology of human psychosexual differentiation. Horm Behav 50:589–601
32. Money J (1981) The development of sexuality and eroticism in humankind. Q Rev Biol 56:379–404
33. Meyer-Bahlburg HF (2010) From mental disorder to iatrogenic hypogonadism: dilemmas in conceptualizing gender identity variants as psychiatric conditions. Arch Sex Behav 39:461–476
34. Hughes IA (2008) Disorders of sex development: a new definition and classification. Best Pract Res Clin Endocrinol Metabol 22:119–134
35. Houk CP, Lee PA (2010) Approach to assigning gender in 46, xx congenital adrenal hyperplasia with male external genitalia: replacing dogmatism with pragmatism. J Clin Endocrinol Metab 95:4501–4508
36. Bao AM, Swaab DF (2011) Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. Front Neuroendocrinol 32:214–226
37. American Psychiatric Association (2013) DSM-5: diagnostic and statistical manual for mental disorders, 5th edn. American Psychiatric Press, Washington, DC
38. Kruijver FP, Zhou JN, Pool CW, Hofman MA, Gooren LJ, Swaab DF (2000) Male-to-female transsexuals have female neuron numbers in a limbic nucleus. J Clin Endocrinol Metab 85:2034–2041
39. Zhou JN, Hofman MA, Gooren LJ, Swaab DF (1995) A sex difference in the human brain and its relation to transsexuality. Nature 378:68–70
40. Smith ES, Junger J, Derntl B, Habel U (2015) The transsexual brain—a review of findings on the neural basis of transsexualism. Neurosci Biobehav Rev 59:251–266
41. Luders E, Sánchez FJ, Gaser C, Toga AW, Narr KL, Hamilton LS, Vilain E (2009) Regional gray matter variation in male-to-female transsexualism. Neuroimage 46:904–907

42. Garcia-Falgueras A, Swaab DF (2008) A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity. Brain 131:3132–3146
43. Berglund H, Lindstrom P, Dhejne-Helmy C, Savic I (2008) Male to female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. Cerebr Cortex 18:1900–1908
44. Gizewski ER, Krause E, Schlamann M, Happich F, Ladd ME, Forsting M, Senf W (2009) Specific cerebral activation due to visual erotic stimuli in male-to-female transsexuals compared with male and female controls: an fMRI study. J Sex Med 6:440–448
45. Burke SM, Menks WM, Cohen-Kettenis PT, Klink DT, Bakker J (2014) Click-evoked otoacoustic emissions in children and adolescents with gender identity disorder. Arch Sex Behav 43:1515–1523
46. Ciocca G, Limoncin E, Cellerino A, Fisher AD, Gravina GL, Carosa E, Mollaioli D, Valenzano DR, Mennucci A, Bandini E, Di Stasi SM, Maggi M, Lenzi A, Jannini EA (2014) Gender identity rather than sexual orientation impacts on facial preferences. J Sex Med 11:2500–2507
47. Hare L, Bernard P, Sànchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR (2009) Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. Biol Psychiatry 65:93–96
48. Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB (2008) A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female to male but not male to female transsexualism. Fertil Steril 90:56–59
49. Henningsson S, Westberg L, Nilsson S, Lundström B, Ekselius L, Bodlund O, Lindström E, Hellstrand M, Rosmond R, Eriksson E, Landén M (2005) Sex steroid-related genes and male-to-female transsexualism. Psychoneuroendocrinology 30:657–664
50. Fisher AD (2013) Disorders of sex development. In: Kirana PS, Tripodi F, Reisman Y, Porst H (eds) The EFS and ESSM syllabus of clinical sexology. Medix publishers, Amsterdam
51. Fisher AD, Ristori J, Bandini E, Giordano S, Mosconi M, Jannini EA, Greggio NA, Godano A, Manieri C, Meriggiola C, Ricca V, Italian GnRH analogs study ONIG group, Dettore D, Maggi M (2014) Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. J Endocrinol Invest 37:675–687
52. Fisk NM (1974) Editorial: gender dysphoria syndrome—the conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen. West J Med 120:386–391
53. Meyer-Bahlburg HF (2005) Introduction: gender dysphoria and gender change in persons with intersexuality. Arch Sex Behav 34:371–373
54. Mayfield W (2001) The development of an internalized homonegativity inventory for gay men. J Homosex 41:53–76
55. Hughes IA, Houk C, Ahmed SF, Lee PA, LWPES Consensus Group; ESPE Consensus Group (2006) Consensus statement on management of intersex disorders. Arch Dis Child 91:554–563
56. Bashamboo A, McElreavey K (2015) Human sex-determination and disorders of sex-development (DSD). Semin Cell Dev Biol 45:77–83
57. McCann-Crosby B, Sutton VR (2015) Disorders of sexual development. Clin Perinatol 42(2):395–412 **(ix–x)**
58. El-Khairi R, Achermann JC (2012) Steroidogenic factor-1 and human disease. Semin Reprod Med 30:374–381
59. Jääskeläinen M, Prunskaite-Hyyryläinen R, Naillat F, Parviainen H, Anttonen M, Heikinheimo M, Liakka A, Ola R, Vainio S, Vaskivuo TE, Tapanainen JS (2010) WNT4 is expressed in human fetal and adult ovaries and its signaling contributes to ovarian cell survival. Mol Cell Endocrinol 317:106–111
60. Tomaselli S, Megiorni F, Lin L, Mazzilli MC, Gerrelli D, Majore S, Grammatico P, Achermann JC (2011) Human RSPO1/R-spondin1 is expressed during early ovary development and augments β-catenin signaling. PLoS ONE 6:e16366
61. Yang JH, Baskin LS, Disandro M (2010) Gender identity in disorders of sex development: review article. Urology 75:153–159
62. DiSandro M, Merke DP, Rink RC (2015) Review of current surgical techniques and medical management considerations in the treatment of pediatric patients with disorders of sex development. Horm Metab Res 47:321–328
63. Ercan O, Kutlug S, Uysal O, Alikasifoglu M, Inceoglu D (2013) Gender identity and gender role in DSD patients raised as females: a preliminary outcome study. Front Endocrinol (Lausanne) 4:86
64. Money J (1975) Ablatio penis: normal male infant sex-reassigned as a girl. Arch Sex Behav 4:65–71
65. Chase C (1998) Surgical progress is not the answer to intersexuality. J Clinical Ethics 9:385–392
66. Bouvattler C, Mignot B, Lefevre H, Morel Y, Bougneres P (2006) Impaired sexual activity in male adults with partial androgen insensitivity. J Clin Endocrinol Metab 91:3310–3315
67. Hooper HT, Figuiredo BC, Pavan-Senn CC, de Lacerca L, Sandrini R, Mengarelli JK, Japp K, Karaviti LP (2004) Concordance of phenotypic expression and gender identity in a large kindred with a mutation in the androgen receptor. Clin Genet 65:183–190
68. Jürgensen M, Kleinemeier E, Lux A, Steemsa TD, Cohen-Kettenis PT, Hiort O, Thyen U, DSD Network Working Group (2010) Psychosexual development in children with disorder of sex development—results from the German Clinical Evaluation Study. J Pediatr Endocrinol Metab 23:565–578
69. Jürgensen M, Lux A, Wien SB, Kleinemeier E, Hiort O, Thyen U (2014) Health-related quality of life in children with disorders of sex development (DSD). Eur J Pediatr 173:893–903
70. Mazur T, Sandberg DE, Perrin MA, Gallagher JA, MacGillivray MH (2004) Male pseudohermaphroditism: long-term quality of life outcome in five 46, XY individuals reared female. J Pediatr Endocrinol Metab 17:809–823
71. Migeon CJ, Wisniewski AB, Gearhart JP, Meyer-Bahlburg HF, Rock JA, Brown TR, Casella SJ, Maret A, Ngai KM, Money J, Berkovitz GD (2002) Ambiguous genitalia with perineo-scrotal hypospadias in 46, XY individuals: long-term medical, surgical and psychosexual outcome. Pediatrics 110:e31
72. Houk CP, Hughes IA, Ahmed SF, Lee PA (2006) Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. Pediatrics 118:753–757
73. van der Zwan YG, Callens N, van Kuppenveld J, Kwak K, Drop SL, Kortmann B, Dessens AB, Wolffenbuttel KP, Dutch Study Group on DSD (2013) Long-term outcomes in males with disorders of sex development. J Urol 190:1038–1042
74. Warne G, Grover S, Hutson J, Sinclair A, Metcalfe S, Northam F, Freeman J, Murdoch Childrens Research Institute Sex Study Group (2005) A long-term outcome study of intersex conditions. J Pediatr Endocrinol Metab 18:555–567
75. Lee PA, Nordenström A, Houk CP, Ahmed SF, Auchus R, Baratz A, Baratz Dalke K, Liao LM, Lin-Su K, Looijenga LH 3rd, Mazur T, Meyer-Bahlburg HF, Mouriquand P, Quigley CA, Sandberg DE, Vilain E, Witchel S, Global DSD update consortium (2016) Global disorders of sex development update since 2006: perceptions, approach and care. Horm Res Paediatr 85:158–180
76. Cheon CK (2011) Practical approach to steroid 5alpha-reductase type 2 deficiency. Eur J Pediatr 170:1–8

77. Cohen-Kettenis PT (2005) Gender change in 46, XY persons with 5alfa-reductase-2 deficiency and 17alpha-hydroxysteroid dehydrogenase-3 deficiency. Arch Sex Behav 34:399–410
78. Nordenström A, Frisén L, Falhammar H, Filipsson H, Holmdahl G, Janson PO, Thorén M, Hagenfeldt K, Nordenskjöld A (2010) A: sexual function and surgical outcome in women with congenital adrenal hyperplasia due to CYP21A2 deficiency: clinical perspective and the patients' perception. J Clin Endocrinol Metab 95:3633–3640
79. Mendonca BB, Domenice S, Arnhold IJ, Costa EM (2009) 46, XY disorders of sex development (DSD). Clin Endocrinol 70:173–187
80. Kim SK, Kim J (2012) Disorder of sex development. Korean J Urol 53:1–8
81. Suresh D, Crawford J, Axelrad ME, Gunn SK, McCullough L, Smith OB, Sutton VR, Roth D, Karaviti LP, Dietrich JE (2013) Assessing sex assignment concordance with genotype and phenotype. Int J Pediatr Endocrinol 2013:7
82. Özbaran B, Özen S, Gökşen D, Korkmaz Ö, Onay H, Özkınay F, Çoğulu Ö, Erermiş S, Köse S, Avanoğlu A, Ulman İ, Darcan Ş (2013) Psychiatric approaches for disorders of sex development: experience of a multidisciplinary team. J Clin Res Pediatr Endocrinol 5:229–235
83. Sandberg D, Mazur T (2014) A non categorical approach to the psychosocial care of persons with DSD and their families. In: Kreukels BP, Steensma TD, de Vries AL (eds) Gender dysphoria and disorders of sex development. Focus on sexuality research. Springer, Berlin, pp 93–114
84. Brook CGD, Clayton P, Brown R (2009) Brook's clinical pediatric endocrinology, 6th edn. Wiley-Blackwell, Hoboken
85. Chowdhury TK, Chowdhury MZ, Mili F, Hutson JM, Banu T (2014) Gender identity shows a high correlation with Prader score in patients with disorders of sex development (DSD) presenting in mid childhood. Pediatr Surg Int 30:527–532
86. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT (2011) Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. Clin Child Psychol Psychiatry 16:499–516
87. Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT (2013) Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry 52:582–590
88. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ (2008) The treatment of adolescent transsexuals: changing insights. J Sex Med 5:1892–1897
89. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfaefflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K (2011) Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgend 13:165–232
90. Hembree WC, Choen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ III, Spack NP, Tangpricha V, Montori VM, Endocrine Society (2009) Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 94:3132–3154
91. Hewitt J, Zacharin M (2015) Hormone replacement in disorders of sex development: current thinking. Best Pract Res Clin Endocrinol Metab 29:437–447
92. Sadjadi S (2013) The endocrinologist's office-puberty suppression: saving children from a natural disaster? J Med Humanit 3:255–260
93. Park R, Consortium on the Management of Disorders of Sex Development (2006) Clinical guidelines for the management of disorders of sex development in childhood. Intersex Society of North America, Whitehouse station, NJ
94. Bukowski WM, McCauley E, Mazur T (2015) Disorders of sex development (DSD): peer relations and psychosocial well-being. Horm Metab Res 47:357–360
95. McCann-Crosby B, Sutton VR (2015) Disorders of sexual development. Clin Perinatol 42:395–412 **(ix–x)**
96. Sandberg DE, Gardner M, Cohen-Kettenis PT (2012) Psychological aspects of the treatment of patients with disorders of sex development. Semin Reprod Med 30:443–452
97. DiSandro M, Merke DP, Rink RC (2015) Review of current surgical techniques and medical management considerations in the treatment of pediatric patients with disorders of sex development. Horm Metab Res 47:321–328
98. Nordenström A (2015) Psychosocial factors in disorders of sex development in a long-term perspective: what clinical opportunities are there to intervene? Horm Metab Res 47:351–356
99. Schweizer K, Brunner F, Handford C, Richter-Appelt H (2014) Gender experience and satisfaction with gender allocation in adults with diverse intersex conditions (divergences of sex development, DSD). Psychol Sex 5:56–82
100. Schönbucher V, Schweizer K, Richter-Appelt H (2010) Sexual quality of life of individuals with disorders of sex development and a 46, XY karyotype: a review of international research. J Sex Marital Ther 36:193–215
101. Chadwick PM, Liao LM, Boyle M (2005) Size matters: experiences of atypical genital and sexual development in males. J Health Psychol 10:529–543
102. Minto CL, Liao KLM, Conway GS, Creighton SM (2003) Sexual function in women with complete androgen insensitivity syndrome. Fertile Steril 80:157–164
103. Suorsa KI, Mullins AJ, Tackett AP, Reyes KJ, Austin P, Baskin L, Bernabé K, Cheng E, Fried A, Frimberger D, Galan D, Gonzalez L, Greenfield S, Kropp B, Meyer S, Meyer T, Nokoff N, Palmer B, Poppas D, Paradis A, Yerkes E, Wisniewski AB, Mullins LL (2015) Characterizing early psychosocial functioning of parents of children with moderate to severe genital ambiguity due to disorders of sex. Development 194:1737–1742
104. Bin-Abbas B, Conte FA, Grumbach MM, Kaplan SL (1999) Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size why sex reversal is not indicated. J Pediatr 134:579–583
105. Chen MJ, Vu BM, Axelrad M, Dietrich JE, Gargollo P, Gunn S, Macias CG, McCullough LB, Roth DR, Sutton VR, Karaviti LP (2015) Androgen insensitivity syndrome: management considerations from infancy to adulthood. Pediatr Endocrinol Rev 12:373–387
106. Palmert MR, Dunkel L (2012) Clinical practice. Delayed puberty. N Engl J Med 366:443–453
107. Lee PA, Houk CP, Ahmed SF, Hughes IA (2006) International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. In: Consensus statement on management of intersex disorders. International consensus conference on intersex. pediatrics, vol 118, pp e488–e500
108. Meyer-Bahlburg HF (2011) Brain development and cognitive, psychosocial, and psychiatric functioning in classical 21-hydroxylase deficiency. Endocr Dev 20:88–95
109. Meyer-Bahlburg HF, Zolezal C, Baker SW, New MI (2008) Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess. Arch Sex Behav 37:85–99

110. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, Meyer-Bahlburg HF, Miller WL, Montori VM, Oberfield SE, Ritzen M, White PC (2010) Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 95:4133–4160
111. Meyer-Bahlburg HF, Dolezal C, Baker SW, Ehrhardt AA, New MI (2006) Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. Arch Sex Behav 35:667–684
112. Berembaum SA, Resnick SM (1997) Early androgen effects on aggression in children and adults with congenital adrenal hyperplasia. Psychoneuroendocrinology 22:505–515
113. Berenbaum SA, Hines M (1992) Early androgen are related to childhood sex-typed toy preferences. Psychol Sci 3:203–206
114. Berenbaum SA, Snyder E (1995) Early hormonal influences on childhood sex-typed activity and playmate development of sexual orientation. Dev Psychol 31:130–136
115. Dittmann RW, Kappes MH, Kappes ME, Borger D, Meyer-Bahlburg HF, Stegner H, Willig RH, Wallis H (1990) Congenital adrenal hyperplasia. I: gender-related behavior and attitudes in female patients and sisters. Psychoneuroendocrinology 15:421–434
116. Slijper FM (1984) Androgens and gender role behavior in girls with congenital adrenal hyperplasia (CAH). Progr Brain Res 61:417–422
117. Ehrardt AA, Meywe-Bahlburg HF (1981) Effects of prenatal sex hormones on gender-related behavior. Science 211:1312–1318
118. Leveroni CL, Berenbaum SA (1998) Early androgens effects on interest in infants: evidence from children with congenital adrenal hyperplasia. Dev Neuropsychol 14:321–324
119. Zucker KJ, Bradely SJ, Olived G, Blake J, Fleming S, Hood J (1996) Psychosexual development of women with congenital adrenal hyperplasia. Horm Behav 30:300–318
120. Pasterski VL, Zucker KJ, Hindmarsh PC, Hughes IA, Acerini CL, Spencer D, Neufeld S, Hines M (2015) Increased cross-gender identification independent of gender role behavior in girls with congenital adrenal hyperplasia: results from a standardized assessment of 4- to 11-year-old children. Arch Sex Behav 44:1363–1375
121. Dittman RW, Kappes ME, Kappes MH (1992) Sexual behavior in adolescent and adult females with congenital adrenal hyperplasia. Pychoneurondocrinology 17:153–170
122. Hines M, Brook C, Conway GS (2004) Androgen and psychosexual development: core gender identity, sexual orientation and recalled childhood gender role behavior in women and men with congenital adrenal hyperplasia (CAH). J Sex Res 41:75–81
123. Kuhnle U, Bullinger M (1997) Outcome of congenital adrenal hyperplasia. Pediatr Surg Int 12:511–515
124. May B, Boyle M, Grant D (1996) A comparative study of sexual experiences: women with diabetes and women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Health Psychol 1:479–492
125. Meyer-Bahlburg HF (1999) What causes low rates of childbearing in congenital adrenal hyperplasia? J Clin Endocrinol Metabol 84:1844–1847
126. Mulaikal RM, Migeon CJ, Rock JA (1987) Fertility rates in female patients with CAH due to 21-hydroxyase deficiency. N Eng J Med 316:178–182
127. Van der Zwag YG, Janssen EH, Callens N, Wolffenbuttel KP, Cohen-Kettenis PT, van de Berg M, Drop SL, Dessens AB, Beerendonk C, Dutch Study Group on DSD (2013) Severity of virilization is associated with cosmetic appearance and sexual function in women with congenital adrenal hyperplasia: a cross-sectional study. J Sex Med 10:866–875
128. Frisen L, Nordenstrom A, Falhammar H, Filipsson H, Holmdahl G, Janson PO, Thorén M, Hagenfeldt K, Möller A, Nordenskjöld A (2009) Gender role behavior, sexuality, and psychosocial adaptation in women with congenital adrenal hyperplasia due to CYP21A2 deficiency. J Clin Endocrinol Metabol 94:3432–3439
129. Dessens AN, Slijper FM, Drop SL (2005) Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Arch Sex Behav 34:389–397
130. Gupta DK, Shilpa S, Amini AC, Gupta M, Aggarwal G, Deepika G, Jamlesh K (2006) Congenital adrenal hyperplasia: long-term evaluation of feminizing genitoplasty and psychosocial aspects. Pediatr Surg Int 22:905–909
131. Meyer-Bahlburg HF, Gruen RS, New MI, Bell JJ, Morishima A, Shimshi M, Bueno Y, Vargas I, Baker SW (1996) Gender change from female to male in classical congenital adrenal hyperplasia. Horm Behav 30:319–332
132. Jorge JC, Echeverri C, Medina Y, Acevedo P (2008) Male gender identity in an XX individual with congenital adrenal hyperplasia. J Sex Med 5:122–131
133. Arlt W, Krone N (2007) Adult consequences of congenital adrenal hyperplasia. Horm Res 68:158–164
134. Berenbaum SA, Bailey JM (2003) Effects on gender identity of prenatal androgens and genital appearance: evidence from girls with congenital adrenal hyperplasia. J Clin Endocrinol Metabol 88:1102–1106
135. Meyer-Balhlburg HF (2009) Male gender identity in a XX individuals with congenital adrenal hyperplasia. J Sex Med 6:297–298
136. Sharma S, Gupta DK (2008) Gender assignment and hormonal treatment for disorders at sexual differentiation. Pediatr Surg Int 24:1131–1135
137. Gupta D, Bharadwaj M, Sharma S, Ammini AC, Gupta DK (2010) Long-term psychosocial adjustment, satisfaction related to gender and the family equations in disorder of sexual differentiation with male sex assignment. Pediatr Surg Int 26:955–958
138. Strandqvist A, Falhammar H, Lichtenstein P, Hirschberg AL, Wedell A, Norrby C, Nordenskjorl A, Frisen L, Nordenstrom A (2014) Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia; epidemiological studies in non-biased national cohort in Sweden. J Clin Endocrinol Metab 99:1425–1432
139. Reisch N, Hahner S, Bleicken B, Flade L, Pedrosa Gil F et al (2011) Quality of life is less impaired in adults with congenital adrenal hyperplasia because of 21-hydroxylase deficiency than in patient with primary adrenal insufficiency. Clin endocrinol (Oxf) 74:166–173
140. Palmer BW, Wisniewski AB, Schaeffer TL, Mallappa A, Tryggestad JB, Krishnan S, Chalmers LJ, Copeland K, Chernausek SD, Reiner WG, Kropp BP (2012) A model of delivering multidisciplinary care to people with 46, XY DSD. J Pediatr Urol 8:7–16
141. McCarty BM, Migeon CJ, Meyer-Bahlburg HF, Zacur H, Wisniewski AB (2006) Medical and psychosexual outcome in women affected by complete gonadal dysgenesis. J Pediatr Endocrinol Metabol 19:873–877
142. Cornet D, Alvarez S, Antoine JM, Tibi C, Mandelbaum J, Plachot M, Salat-Baroux J (1990) Pregnancy following ovum donation in gonadal dysgenesis. Hum Reprod 5:291–293
143. Michala L, Goswami D, Creighton SM, Conway GS (2008) Swyer syndrome: presentation and outcomes. BJOG 115:737–741
144. Kan AJ, Abdalla JI, Oscarsson T (1997) Two successful pregnancies in 46, XY patient. Hum Reprod 12:1434–1435

145. Plante BJ, Fritz MA (2008) A case report of successful pregnancy in a patient with pure 46, XY gonadal dysgenesis. Fertil Steril 90:2015.e1–2015.e2
146. Selvaraj K, Ganesh V, Selvaraj P (2002) Successful pregnancy in a patient with a 46, XY karyotype. Fertil Steril 78:419–420
147. Cools M, Looijenga LH, Wollfenbuttel KP, Drop SL (2009) Disorders of sex development: update on the genetic background, terminology and risk for the development of germ cell tumors. Worl J Pediatr 5:93–102
148. Migeon CJ, Krishnan S, Wisniewski AB (2007) Ambiguous genitalia in the newborn. In: Pediatric endocrinology, 1st edn, Chap. 16. http://www.endotext.org/pediatrics/pediatrics10/pediatricsframe10.htm
149. Mazur T (2005) Gender dysphoria and gender changes in androgen insensitivity or micropenis. Arch Sex Behav 34:411–421
150. Hughes IA, Davies JD, Bunch TI, Pasterski V, Mastroyannopoulou K, MacDougall J (2012) Androgen insensitivity syndrome. Lancet 380:1419–1428
151. Liu AX, Shi HY, Cai ZJ, Liu A, Zhang D, Huang HF, Jin HM (2014) Increased risk of gonadal malignancy and prophylactic gonadectomy: a study of 102 phenotypic female patients with Y chromosome or Y-derived sequences. Hum Reprod 29:1413–1419
152. Nakhal RS, Hall-Craggs M, Freeman A, Kirkham A, Conway GS, Arora R, Woodhouse CR, Wood DN, Creighton SM (2013) Evaluation of retained testes in adolescent girls and women with complete androgen insensitivity syndrome. Radiology 268:153–160
153. Masica DN, Money J, Ehrhardt AA (1971) Fetal feminization and female gender identity in the testicular feminizing syndrome of androgen insensitivity. Arch Sex Behav 1:131–142
154. Hines M, Ahmed SF, Hughes IA (2003) Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. Arch Sex Behav 32:93–101
155. Melo KF, Menodanca BB, Billerbeck AE, Costa EM, Inacio M, Silva FA, Leal AM, Latronico AC, Arnhold IJ (2003) Clinical, hormonal, behavioral and genetic characteristics of androgen insensitivity syndrome in a Brazilian cohort: five novel mutations in the androgen receptor gene. J Clin Endocrinol Metab 88:3241–3250
156. Jürgensen M, Hiort O, Holterhus PM, Thyen U (2007) Gender role behavior in children with XY karyotype and disorders of sex development. Horm Behav 51:443–453
157. Kulshreshtha B, Philibert P, Eunice M, Khandelwal SK, Mehta M, Audran F, Paris F, Sultan C, Ammini AC (2009) Apparent male gender identity in a patient with complete androgen insensitivity syndrome. Arch Sex Behav 38:873–875
158. T'Sjoen G, De Cuypere G, Monstray S, Hoebeke P, Freedman FK, Appari M, Holterhus PM, Van Borsel J, Cools M (2011) Male gender identity in complete androgen insensitivity syndrome. Arch Sex Behav 40:635–638
159. Herdt GH, Davidson J (1988) The Sambia "turnim-man": sociocultural and clinical aspects of gender formation in male pseudohermaphrodites with 5-alpha-reductase deficiency in Papua New Guinea. Arch Sex Behav 17:33–56
160. Ademola Akesode F, Meyer WJ, Migeon CJ (1977) Male pseudohermaphroditism with gynecomastia due to testicular 17-ketosteroid reductase deficiency. Clin Endocrinol (Oxf) 7:443–452
161. Bertelloni S, Dati E, Hiort O (2009) Diagnosis of 17beta-hydroxysteoid dehydrogenase deficiency. Expert Rev Endocrinol Metab 4:53–65
162. Hiort O, Renecke S, Thyen U, Jürgensen M, Holterhus PM, Schön D, Richter-Appelt H (2003) Puberty in disorders of somatosexual differentiation. J Pediatr Endocrinol Metab 16:297–306
163. Boehemer AL, Brinkmann AO, Sandjuij LA, Halleym DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL (1999) 17beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics and word wide distribution of ancient and de novo mutations. J Clin Endocrinol Metab 84:4713–4721
164. Galdiero M, Vitale P, Simeoli C, Afeltra L, Melis D, Alviggi C, Cariati F, Lo Calzo F, Di Somma C, Colao A, Pivonello R (2013) The 17β-hydroxysteroid dehydrogenase type 3 deficiency: a case report of an 18-year patient and review of the literature. Minerva Endocrinol 38:113–122
165. Jürgensen M, Hampel E, Hiort O, Thyen U (2006) "Any decision is better than none" decision-making about sex of rearing for siblings with 17beta-hydroxysteroid-dehydrogenase-3 deficiency. Arch Sex Behav 35:359–571
166. Mendonca BB, Inacio M, Arnhold IJ, Costa EM, Bloise W, Martin RM, Denes FT, Silva FA, Andersson S, Lindqvist A, Wilson JD (2000) Male pseudohermaphroditism due to 17beta-hydroxysteroid dehydrogenase-3 deficiency. Diagnosis, psychological evaluation, and management. Medicine (Baltimore) 79:299–309
167. Rosler A (1992) Steroid 17beta-hydroxysteroid dehydrogenase-3 deficiency in man: an inherited form of male pseudohermaphroditism. J Steroid Biochem Mol Biol 43:989–1002
168. Chuang J, Vallerie A, Breech L, Saal HM, Alam S, Crawford P, Rutter MM (2013) Complexities of gender assignment in 17β-hydroxysteroid dehydrogenase type 3 deficiency: is there a role for early orchiectomy? Int J Pediatr Endocrinol 2013:15
169. Deeb A, Mason C, Lee YS, Hughes IA (2005) Correlation between genotype, phenotype and sex of rearing in 111 patients with partial androgen insensitivity syndrome. Clin Endocrinol (Oxf) 63:56–62
170. Joseph AA, Shabir I, Marumadi E, Dada R, Ammini AC, Mehta M (2013) Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. J Pediatr Endocrinol Metabol 26:915–920
171. Money J, Onguro C (1974) Behavioral sexology: ten cases of genetic male intersexuality with impaired prenatal and pubertal androgenization. Arch Sex Behav 3:181–205
172. Lee PA, Houk CP (2004) Outcome studies among men with micropenis. J Pediatr Endocrinol Metab 17:1043–1053
173. Callens N, Hoebeke P (2014) Phalloplasty: a panacea for 46, XY disorders of sex development conditions with penile deficiency? Endocr Dev 24:222–233
174. Callens N, De Cuypere G, T'Sjoen G, Monstrey S, Lumen N, Van Laecke E, Hoebeke P, Cools M (2014) Sexual quality of life after total phalloplasty in men with penile deficiency: an exploratory study. World J Urol 33:137–143
175. Callens N, De Cuypere G, Van Hoecke E, T'Sjoen G, Monstrey S, Cools M, Hoebeke P (2013) Sexual quality of life after hormonal and surgical treatment, including phalloplasty in men with micropenis: a review. J Sex Med 10:3006–3018
176. Reilly JM, Woodhouse CR (1989) Small penis and male sexual role. J Urol 142:569–571
177. Diamond M, Sigmudson HK (1997) Management of intersexuality. Guidelines for dealing with persons with ambiguous genitalia. Arch Pediatr Adolesc Med 151:1046–1105
178. Reiner WG (1997) Sex assignment in the neonate with intersex or inadequate genitalia. Arch Pediatr Adolesc Med 151:1044–1045
179. Meyer-Bahlburg HF (2005) Gender identity outcome in female raised 46 XY persons with penile agenesis, cloacal exstrophy of the bladder or penile ablation. Arch Sex Behav 34:423–438

180. Reiner WG, Gearhart JP (2004) Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. N Eng J Med 350:333–341
181. Diamond DA, Burns JP, Huang L, Rosoklija I, Retik AB (2011) Gender assignment for newborns with 46XY cloacal exstrophy: a 6-year followup survey of pediatric urologists. J Urol 186:1642–1648
182. Schonbucher VB, Landolft MA, Gobert R, Weber DM (2008) Psychosexual development of children and adolescents with hypospadias. J Sex Med 5:1365–1373
183. Sandberg DE, Meyer-Bahlburg HF, Yager TJ, Hensle TW, Levitt SB, Kogan SJ, Reda EF (1995) Gender development in boys born with hypospadias. Psychoneuroendocrinology 20:693–709
184. Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G (2011) Karyotyping, is it worthwhile in transsexualism? J Sex Med 8:475–478
185. Maeda T, Ohno M, Matsunobu A, Yoshihara K, Yabe N (1991) A cytogenetic survey of 14,835 consecutive liveborns. Jinrui Idengaku Zasshi 36:117–129
186. Fisher AD, Castellini G, Casale H, Fanni E, Bandini E, Campone B, Ferruccio N, Maseroli E, Boddi V, Dèttore D, Pizzocaro A, Balercia G, Oppo A, Ricca V, Maggi M (2015) Hypersexuality, paraphilic behaviors, and gender dysphoria in individuals with Klinefelter's syndrome. J Sex Med 12:2413–2424
187. Hughes IA, Deeb A (2006) Androgen resistance. Best Pract Res Clin Endocrinol Metab 20:577–598
188. Kolesinska Z, Ahmed SF, Niedziela M, Bryce J, Molinska-Glura M, Rodie M, Jiang J, Sinnott RO, Hughes IA, Darendeliler F, Hiort O, van der Zwan Y, Cools M, Guran T, Holterhus PM, Bertelloni S, Lisa L, Arlt W, Krone N, Ellaithi M, Balsamo A, Mazen I, Nordenstrom A, Lachlan K, Alkhawari M, Chatelain P, Weintrob N (2014) Changes over time in sex assignment for disorders of sex development. Pediatrics 134:e710–e715
189. Cox K, Bryce J, Jiang J, Rodie M, Sinnott R, Alkhawari M, Arlt W, Audi L, Balsamo A, Bertelloni S, Cools M, Darendeliler F, Drop S, Ellaithi M, Guran T, Hiort O, Holterhus PM, Hughes I, Krone N, Lisa L, Morel Y, Soder O, Wieacker P, Ahmed SF (2014) Novel associations in disorders of sex development: findings from the I-DSD registry. J Clin Endocrinol Metab 99:348–355
190. Hiort O, Wünsch L, Cools M, Looijenga L, Cuckow P (2012) Requirements for a multicentric multidisciplinary registry on patients with disorders of sex development. J Pediatr Urol 8:624–628