UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

5 α -Reductase-2 deficiency: is gender assignment recommended in infancy? Two case-reports and review of the literature

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

5 α -Reductase-2 deficiency: is gender assignment recommended in infancy? Two case-reports and review of the literature / Cocchetti C, Ristori J, Mazzoli F, Prunas A, Bertelloni S, Magini A, Vignozzi L, Maggi M, Fisher AD. - In: JOURNAL OF ENDOCRINOLOGICAL INVESTIGATION. - ISSN 1720-8386. - STAMPA. - 43:(2020), pp. 1131-1136. [10.1007/s40618-020-01193-w]

Availability:

This version is available at: 2158/1188039 since: 2020-10-19T13:07:28Z

Published version:

DOI: 10.1007/s40618-020-01193-w

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

(Article begins on next page)

5 α -Reductase-2 deficiency: is gender assignment recommended in infancy? Two case-reports and review of the literature

C. Cocchetti¹ · J. Ristori¹ · F. Mazzoli¹ · A. Prunas² · S. Bertelloni³ · A. Magini¹ · L. Vignozzi¹ · M. Maggi⁴ · A. D. Fisher¹

Received: 19 November 2019 / Accepted: 30 January 2020
© Italian Society of Endocrinology (SIE) 2020

Abstract

Purpose Gender assignment represents one of the most controversial aspects of the clinical management of individuals with Differences of Sex Development, including 5 α -Reductase-2 deficiency (SRD5A2). Given the predominant female appearance of external genitalia in individuals with SRD5A2 deficiency, most of them were assigned to the female sex at birth. However, in the last years the high rate of gender role shift from female to male led to recommend a male gender assignment.

Methods We here describe two cases of subjects with SRD5A2 deficiency assigned as females at birth, reporting their clinical histories and psychometric evaluations (Body Uneasiness Test, Utrecht Gender Dysphoria Scale, Bem Sex-Role Inventory, Female Sexual Distress Scale Revised, visual analogue scale for gender identity and sexual orientation) performed at the time of referral at the Florence Gender Clinic.

Results Both patients underwent early surgical interventions without being included in the decision-making process. They had to conform to a binary feminine gender role because of social/familiar pressure, with a significant impact on their psychological well-being. Psychometric evaluations identified clinically significant body uneasiness and gender incongruence in both subjects. No sexually related distress and undifferentiated gender role resulted in the first subject and sexually related distress and androgynous gender role resulted in the second subject.

Conclusions The reported cases suggest the possibility to consider a new approach for gender assignment in these individuals, involving them directly in the decision-making process and allowing them to explore their gender identity, also with the help of GnRH analogues to delay pubertal modifications.

Keywords Differences of sex development · Gender assignment · GnRH analogues · 5 α reductase-2 deficiency

Introduction

Steroid 5 α -Reductase-2 (SRD5A2) deficiency is an autosomal-recessive form of 46,XY Differences of Sex Development (DSD) [1, 2] caused by pathogenetic variants in the SRD5A2 gene located on chromosome 2p23.1 [3, 4]. This

gene encodes the enzyme that converts testosterone (T) into the more active metabolite dihydrotestosterone (DHT) [3, 5]. The impaired activity of this enzyme results in variable impairment of DHT synthesis, depending on its residual activity. During foetal development, DHT is required for the male virilization of the external genitalia; then, DHT drives the development of male secondary sexual characteristics at puberty [6]. The phenotype of affected newborns may significantly differ on the basis of the enzyme activity within a wide spectrum of manifestations, ranging from almost female external genitalia to undervirilized male genitalia, including penile hypospadias and isolated micropenis [3, 6]. Due to normal anti-müllerian hormone (AMH) and T levels during prenatal period, individuals with SRD5A2 deficiency are characterized by the absence of müllerian structures and by the presence of male internal reproductive structures, with testes usually located in the inguinal or labioscrotal region [3, 7–10].

✉ A. D. Fisher
alessandra.fisher@aou-careggi.toscana.it

¹ Andrology, Women's Endocrinology and Gender Incongruence Unit, University of Florence, Florence, Italy

² Department of Psychology, University of Milano-Bicocca, Milan, Italy

³ Pediatric Division, Department of Obstetrics, Gynecology and Pediatrics, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy

⁴ Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

The biochemical pattern is characterized by a normal-to-high male serum concentrations of T, low or low normal concentrations of DHT and increased T/DHT ratio [3]. However, this pattern may be equivocal and its interpretation is not always easy, especially in individuals with partial enzyme deficiency. In these cases, direct genetic testing of the SRD5A2 gene may represent a useful approach to confirm diagnosis [11].

Regarding gender assignment at birth, several individuals are raised as girls at least in Western countries, since ambiguous genitalia and clitoromegaly represent the most frequent genital phenotype in affected newborns [12]. However, 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, resulting from the residual enzyme activity of SRD5A2 or the action of SRD5 type 1 enzyme stimulated by the increasing concentration of T [7, 10]. Among persons assigned to female sex, in adolescence or young adulthood is reported a high rate (56–63%) of gender role switch from female to male [13].

We here describe two persons with SRD5A2 deficiency assigned to female sex at birth, reporting their clinical histories and psychometric evaluations assessed at the time of the referral to our clinic. They both underwent early surgical interventions to “normalize” external genitalia under parental and health professional’s recommendation. They discovered their true condition only in late adolescence-adulthood and were not included in the decision-making process, resulting in significant impact on their psychological well-being. We asked these patients to complete different psychometric questionnaires, including the Body Uneasiness Test (BUT) [14], the Utrecht Gender Dysphoria Scale (Utrecht GD) [15] and the Bem Sex-Role Inventory (BSRI) [16] to assess body uneasiness, gender dysphoria and gender role, respectively. In addition, sexually related distress was measured by the Female Sexual Distress Scale Revised (FSDS-R) [17]. Finally, a visual analogue scale (VAS) for gender identity and sexual orientation was used, to dimensionally assess these dimensions [18]. The VAS gender identification with the opposite genotypic sex ranges from 0 when the subject has an absolute identification with the opposite genotypic sex to 10 when the identification was with their own genotypic sex. The VAS for sexual attraction towards men or women rates 0, 10 and > 0 and < 10 when the subject has a homosexual, heterosexual or bisexual sexual orientation, respectively.

The study protocol was approved by the Institution’s Ethics Committee and patients have provided their informed consent.

Patients and methods

Case 1- (S.)

S. was born in 1977 from non-consanguineous parents without family history of ambiguous genitalia or atypical sexual development. She was assigned female at birth based on apparently female external genitalia. At the age of 2 months, physical examination showed clitoral and labia majora hypertrophy and ectopic external urethral meatus. Bilateral palpable testes were located in the inguinal region, descending at the level of labioscrotal folds. The karyotype analysis confirmed a normal 46,XY chromosomal pattern and uretrovaginography revealed a 2 cm deep blind-ending vaginal duct. At that time, a diagnosis of androgen insensitivity syndrome was formulated. Informed of possible risks derived from potential gonadal malignancy, parents decided to confirm female gender assignment. At the age of five, S. underwent bilateral gonadectomy, clitoroplasty and vulvoplasty with removal of cavernous bodies. During her childhood years, the mother pressed S. to conform to a rigidly “feminine” gender role: this implied, for example, not allowing the daughter to show interest in sports or hobbies that were considered “too masculine”. The patient started oestrogen replacement treatment when she was 12 years old.

She underwent the last surgery (colonvaginoplasty) in 1996, when she was 19 years old; during her first sexual intercourse, she had experienced pain, and, only then, she was informed on her condition and the opportunity to create a deep-enough vagina.

The truth about her being intersex brought about a lot of resentment towards her parents, and also towards the surgeon who operated on her.

S. found out that, over the years, the father had collected a lot of information about her condition, but he never talked to her openly.

Deep feelings of shame, a vague sense of “uneasiness” she had experienced all her life, and the family’s secrecy over her condition led her to try cocaine until she got addicted. Cocaine was also used to make sexual intercourses with male partners less painful at to feel more at ease in her sexual role.

She showed severe impulsivity (which, besides drug use, led her to binge eating and shoplifting), till she finally decided to enter a therapeutic community where she was treated with psychotherapy and psychiatric care.

When S. was 30 years old, a SRD5A2 sequencing revealed a compound heterozygosis for two variants (p.A207D in exon 4 and p.Y235F in exon 5). No mutations were found in the androgen receptor gene. At the time of the referral to our clinic, the patient was 40 and

was no longer taking oestrogen replacement treatment and physical examination revealed a Ferriman Gallwey score 0 [19], normoconformed labia and a hypo-represented clitoris due to early surgery.

Psychometric evaluations completed at the time of the referral showed high levels of body uneasiness (BUT-Global Severity Index 1.91) and the absence of sexually related distress (FSDS score 0). The patient scored 42/60 at the Utrecht Gender Dysphoria Scale. Visual analogue scale for gender identity and sexual orientation resulted in gender variant identity and bisexual orientation (5.1 and 5.4 cm respectively). Concerning gender role (BSRI), the patient scored 2.90 on masculinity and 3.80 on femininity scores, resulting in undifferentiated gender role.

Case 2-(M.)

M. was born from a Caucasian non-consanguineous couple and was assigned to female sex at birth despite physical examination revealed ambiguous genitalia with separate vaginal and urethral openings, as well as clitoromegaly. At the age of 12, M. experienced pubertal changes characterized by deepening of voice, body hair growth and increase of the clitoris size with the absence of breast development. Ultrasound imaging identified the presence of testes in the inguinal region. At that time, an hCG stimulation test was performed according to standard protocols (2000 IU/i.m. daily for 3 consecutive days with sampling at days 0, 3 and 5). The peak testosterone/DHT ratio suggested SRD5A2 deficiency (22), considering a cut-off value of 10 [10, 20]. However, the patient received a diagnosis of androgen insensitivity syndrome. Given the external genital phenotype, physicians recommended a female sex assignment and bilateral removal of gonads, according to the parents' preference. At the age of 13, gonadectomy and vaginoplasty were performed. Increasing doses of oestrogens were started to induce female puberty and then progestogens were added. Probably the patient also underwent clitoroplasty, but no medical records of the latter surgical correction are available. Histological analysis on the removed testes excluded evidences of malignancy.

Like S., during her adolescence, M. was constantly pressed to conform to a rigidly "feminine" gender role. In addition, she was asked to "control" her voice while in public, to avoid embarrassing situations for the family.

At the age of 20, M. discovered her intersex condition, after finding her medical records hidden by parents. She feels anger towards her family and healthcare providers, who kept this condition secret until adulthood, excluding her from the decision-making process.

Shame for her body (i.e. her height, clitoris size and deep voice) was an issue for her all her life, and had a significant impact on her relational and sexual well-being.

At the time of the referral to our clinic, the patient was 42 and she was taking oestrogen/progestin replacement hormone therapy. Physical examination revealed Ferriman Gallwey score 3 [19], normoconformed labia and clitoris length of 5.4 cm with a diameter of 1.6 cm [21]. SRD5A2 deficiency was considered during the diagnostic process and SRD5A2 was sequenced revealing the presence of heterozygous pathogenic variants in SRD5A2 gene (p.Gly183Ser and p.Leu111Hisfs*24), already reported in the literature [22, 23]. No duplications/deletions of genes DMRT1 (doublesex and mab-3 related transcription factor 1), CYP17A1 (cytochrome P450 family 17 subfamily A member 1), SRD5A2 and HSD17B3 (hydroxysteroid 17-beta dehydrogenase 3) were identified.

Psychometric evaluations identified the presence of a clinically significant body uneasiness (BUT GSI 1.65), sexually related distress (FSDS total score 25) and an androgynous gender role (BSRI scores 4.80 on masculinity and 5.30 on femininity). The patient scored 34/60 at the Utrecht Gender Dysphoria Scale. Visual analogue scale for gender identity and sexual orientation rated 2.4 and 3.2 cm, respectively.

Discussion

Gender assignment represents one of the most critical aspects in the clinical management of newborns with DSD diagnosis. As DSD are a rare condition, in the literature very few studies explored outcomes regarding gender identity, gender role identification and sexual orientation in this population [24–32]. Common beliefs concerning gender assignment in DSD individuals have deeply changed in the last years [33]. In the past, Money [34] postulated the "optimal gender policy", based on the idea that gender identity was completely neutral at birth and developed only in the postnatal period with the influence of social, familiar and cultural factors. According to this theory, if a child with an intersex condition was raised without gender ambiguity supported by hormonal treatment at puberty and early surgical interventions, gender identity was expected to develop in line with the assigned sex. This approach did not contemplate the patient's participation in the decision-making process and parents were advised not to discuss the intersex state with their child, keeping the condition in secret [35], as here reported. This approach led to early gender assignments and surgical corrections of atypical genitalia according to assigned sex. In fact, gender assignment was mainly based on expected surgical outcomes and aimed "to normalize" the ambiguous genitalia, allowing an adequate sexual functioning in late adolescence/adulthood. Since most newborns with SRD5A2 deficiency present with female appearance of external genitalia, they were usually assigned to female sex at birth and raised as girls to ensure a proper sexual

functioning. However, as in Case 2, female gender assignment at birth does not necessarily lead to a satisfying sexuality, since sexual well-being results from interactions among organic, intrapsychic and relational factors.

In recent years, the clinical management of this condition has been revolutionized by the new conception of psychosexual development, as the result of genetic, hormonal and psychosocial influences [36, 37]. This was confirmed by increasing evidences regarding high rates of gender dysphoria (56–63%) in individuals with SRD5A2 deficiency assigned as females at birth [13]. The high rate of gender role switch from female to male during puberty may be partly explained by the prenatal exposition of the brain to androgens. Other factors involved could be represented by cultural and environmental pressures, body image and body changes occurring during puberty. For this reason, nowadays male gender assignment—in line with genetic and gonadal sex—is normally recommended in individuals with SRD5A2 deficiency, despite the possibly female appearance of external genitalia at birth [1]. Other factors may explain the recommendation for male gender assignment. First of all, fertility potential became an important issue to evaluate before performing early gonadal removal [38, 39], as specific techniques of assisted reproduction could be performed in these subjects. Furthermore, new evidences showed that the gonadal cancer risk is low in those who did not undergo orchiectomy and does not seem sufficient to recommend early gonadectomy, since regular testicular evaluation could be an adequate approach [40, 41]. Finally, the past recommendation for female assignment on the basis of surgical outcomes seems to be overcome by the improvement of male reconstructive surgical techniques.

However, in line with the two cases reported here, other examples of individuals with SRD5A2 deficiency raised as females who did not experience gender dysphoria and did not decide to undergo a gender-affirming path later in life are reported in the literature [10, 13, 30, 31, 42]. This underlines the fact that male gender identity does not necessarily represent the rule in these subjects. Since the advancement of molecular technologies and the increase of knowledge about DSD among healthcare professionals have led and will lead more and more to an early diagnosis, the clinical management of these individuals should be reconsidered.

Bearing in mind that every subject with DSD is unique and should be treated with individualized care by a multidisciplinary team (including an endocrinologist, a mental health professional, surgeons, an ethicist and a geneticist), it could be appropriate to delay gender assignment at the time the person is able to explore and express his gender identity and to actively participate in the decision-making process. This applies above all to the timing of genital surgery, to avoid early irreversible surgical corrections, which represent an abuse of human rights of these persons [43]. In this

perspective, families should be largely counselled regarding possible concerns about early and late gender assignment. We would like to stress the opportunity to evaluate the use of gonadotropin-releasing hormone analogues (GnRHa) in adolescents with a diagnosis of DSD. As in gender dysphoric adolescents [44], GnRHa may represent a useful approach to temporary suspend puberty, allowing to arrest pubertal body changes and preventing irreversible changes due to virilization. In fact, puberty in these adolescents may be traumatic, inducing important changes in external appearance up to the switch in the phenotypic sex. GnRHa could allow the adolescent to gain time to explore his gender identity and actively participate in the decision on gender assignment.

In conclusion, the cases presented underline the complexity of clinical management of newborns with a diagnosis of DSD particularly SRD5A2 deficiency— and the criticalities of early gender assignment in these individuals. We would like to stress the idea that current recommendations based on small evidences may not be generalizable to all patients. In our opinion, it may be time to consider a new approach for gender assignment in these patients, involving them directly in the decision-making process and allowing them to explore their gender identity, even with the help of GnRHa during adolescence.

Acknowledgement Dr. Cindy Degli Innocenti o Cresciuti has been acknowledged for data collection.

Compliance with ethical standards

Conflict of interest The authors have no potential conflict of interest.

Ethical approval The study protocol was approved by the Institution's Ethics Committee.

Informed consent All patients included in this study provided their informed consent.

References

1. Hughes I, Houk C, Ahmed SF, Lee PA, LWEPS Consensus Group, ESPE Consensus Group (2006) Consensus statement on management of intersex disorders. *Arch Dis Child* 91:554–563
2. Sandberg DE, Gardner M, Callens N, Muzur T, DSD-TRN Psychosocial Workgroup, the DSD-TRN Advocacy Advisory Network, and Accord Alliance (2017) Interdisciplinary care in disorders/differences of sex development (DSD). The psychosocial component of the DSD-Translational research network. *Am J Med Genet C* 175(2):279–292
3. Wilson JD, Griffin JE, Russell DW (1993) Steroid 5 α -reductase 2 deficiency. *Endocr Rev* 14:577–593
4. Wigley WC, Prihoda JS, Mowszowicz I, Mendonca BB, New MI et al (1994) Natural mutagenesis study of the human steroid 5 α -reductase 2 isozyme. *Biochemistry* 33:1265–1270
5. Cheon CK (2011) Practical approach to steroid 5 α -reductase type 2 deficiency. *Eur J Pediatr* 170:1–8

6. Imperato-McGinley J et al (1974) Steroid 5 α -reductase deficiency in men: an inherited form of male pseudohermaphroditism. *Science* 186(4170):1213–1215
7. Imperato-McGinley J, Peterson RE, Gautier T, Sturla E (1979) Male pseudohermaphroditism secondary to 5 α -reductase deficiency: a model for the role of androgens in both the development of the male phenotype and the evolution of a male gender identity. *J Steroid Biochem Mol Biol* 11:37–45
8. Hiort O, Reinecke S, Thyen U, Jürgensen M, Holterhus PM et al (2003) Puberty in disorders of somatosexual differentiation. *J Pediatr Endocrinol Metab* 16:297–306
9. Sinnecker GH, Hiort O, Dibbelt L, Albers N, Dorr HG et al (1996) Phenotypic classification of male pseudohermaphroditism due to steroid 5 α -reductase 2 deficiency. *Am J Med Genet* 63:223–230
10. Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P et al (2011) Phenotypical, biological, and molecular heterogeneity of 5 α -reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab* 96:296–307
11. Chan AO, But BW, Lee CY, Lam YY, Ng KL et al (2013) Diagnosis of 5 α -reductase 2 deficiency: is measurement of dihydrotestosterone essential? *Clin Chem* 59:798–806
12. Fisher AD, Ristori J, Fanni E, Castellini G, Forti G, Maggi M (2016) Gender identity, gender assignment and reassignment in individuals with disorders of sex development: a major dilemma. *J Endocrinol Invest* 39(11):1207–1224
13. Cohen-Kettenis PT (2005) Gender change in 46, XY persons with 5 α -reductase-2 deficiency and 17 α -hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav* 34:399–410
14. Cuzzolaro M, Vetrone G, Marano G, Battacchi MW (1999) BUT, Body Uneasiness test: anewattitudinal body image scale. *Psichiatri Infanz Adolesc* 66:417–428
15. Cohen-Kettenis PT, van Goozen SH (1997) Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry* 36(2):263–271
16. Bem SL (1974) The measurement of psychological androgyny. *J Consult Clin Psychol* 2:155–162
17. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y (2008) Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. *J Sex Med* 5(2):357–364
18. 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(2):2413–2424
19. Yildiz BO, Bolour S, Woods K, Moore A, Azziz R (2010) Visually scoring hirsutism. *Hum Reprod Update* 16:51–64
20. Bertelloni S, Russo G, Baroncelli GI (2018) Human Chorionic Gonadotropin test: old uncertainties, new perspectives, and value in 46, XY Disorders of Sex Development. *Sex Dev* 12:41–49
21. Verkauf BS, Von Thron J, O'Brien WF (1992) Clitoral size in normal women. *Obstet Gynecol* 80:41–44
22. Thigpen AE, Davis DL, Milatovich A, Mendonca BB, Imperato-McGinley J, Griffin JE, Francke U, Wilson JD, Russell DW (1992) Molecular genetics of steroid 5 α -reductase 2 deficiency. *J Clin Invest* 90(3):799–809
23. Bertelloni S, Baldinotti F, Russo G, Ghirri P, Dati E, Michelucci A, Moscuza F, Meroni S, Colombo I, Sessa MR, Baroncelli GI (2016) 5 α -Reductase-2 Deficiency: clinical findings, endocrine pitfalls, and genetic features in a large Italian cohort. *Sex Dev* 10(1):28–36
24. Bouvattier 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
25. Hooper HT, Figueredo BC, Pavan-Senn CC, de Lacerda 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
26. 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
27. 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
28. 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
29. 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
30. Byers HM, Mohnach LH, Fechner PY, Chen M, Thomas IH, Ramsdell LA, Shnorhavorian M, McCauley EA, Amies Oelschlager AE, Park JM, Sandberg DE, Adam MP, Keegan CE (2017) Unexpected ethical dilemmas in sex assignment in 46, XY DSD due to 5-alpha reductase type 2 deficiency. *Am J Med Genet C* 175(2):260–267
31. Kreukels BPC, Köhler B, Nordenström A, Roehle R, Thyen U, Bouvattier C, de Vries ALC, Cohen-Kettenis PT, dsd-LIFA group (2018) Gender dysphoria and gender change in disorders of sex development/intersex conditions: results from the dsd-LIFE Study. *J Sex Med* 15(5):777–785
32. Khorashad BS, Aghili Z, Kreukels BP et al (2016) Psychosexual outcome among Iranian individuals with 5 α -reductase deficiency type 2 and its relationship with parental sexism. *J Sex Med* 13:1629–1641
33. Kolesinska Z, Ahmed SF, Niedziela M, Bryce J, Molinska-Glura M, Rodie M, Weintrob N (2014) Changes over time in sex assignment for disorders of sex development. *Pediatrics* 134(3):e710–e715
34. Money J (1975) Ablatio penis: normal male infant sex-reassigned as a girl. *Arch Sex Behav* 4(1):65–71
35. Yang JH, Baskin LS, Disandro M (2010) Gender identity in disorders of sex development: review article. *Urology* 75:153–159
36. 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.
37. 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
38. Lee PA, Nordenström A, Houk CP, Ahmed SF, Auchus R, Baratz A, Baratz Dalke K, Liao LM, Lin-Su K, Looijenga III LH, 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
39. Mendonca BB, Domenice S, Arnhold JJ, Costa EM (2009) 46, XY disorders of sex development (DSD). *Clin Endocrinol* 70:173–187
40. Sasaki G, Nakagawa K, Hashiguchi A, Hasegawa T, Ogata T, Murai M (2003) Giant seminoma in a patient with 5 α -reductase type 2 deficiency. *J Urol* 169(3):1080–1081
41. 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. *World J Pediatr* 5:93–102
42. Nascimento RLP, de Andrade-Mesquita IM, Gondim R, Dos Apçstolos RAAC, Toralles MB, de Oliveira LB, Canguçu-Campinho AK, Barroso U Jr (2018). Gender identity in patients with 5-alpha reductase deficiency raised as females. *J Pediatr Urol* 14(5):419e1–419e6.
43. 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
44. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen G (2017) Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 102(11):3869–3903

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.