Psychosexual Outcome Among Iranian Individuals With 5α-Reductase Deficiency Type 2 and Its Relationship With Parental Sexism

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ABSTRACT

Introduction: Few studies exist on the psychosexual outcome of homogeneous groups of individuals with 5α-reductase deficiency type 2 (5α-RD-2) and the relation between gender changes and parental hostile and benevolent sexism, which are two components of ambivalent sexism that assume a stereotypical approach toward women in an overtly negative way or a chivalrous, seemingly positive way.

Aim: To report on the psychosexual outcome of individuals with 5α-RD-2 and to investigate its relation to the level of parental sexism in a relatively large sample of Iranians with 5α-RD-2.

Methods: Twenty participants (mean age = 19.5 years, SD = 6.345) with a molecularly confirmed diagnosis of 5α-RD-2 who were assigned the female gender at birth and raised as female were included in the study. Participants and their parents were interviewed and their medical records were assessed. Parents also completed the Ambivalent Sexism Inventory (ASI), which includes hostile and benevolent sexism subscales.

Main Outcome Measures: Psychosexual outcome and parental hostile and benevolent sexism measurements.

Results: Twelve of 20 participants (60%) were diagnosed with gender identity disorder not otherwise specified (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision). Ten of these transitioned to the male gender. The other 10 participants (50%), including the two diagnosed with gender identity disorder not otherwise specified, continued living in a female gender role. When comparing the ASI subscale scores between families of participants who changed their gender and those who did not, no significant difference was found for ASI total and hostile sexism scores, but there was a difference for benevolent sexism (P = .049): those whose daughters had changed their gender had higher benevolent sexism scores.

Conclusion: The high prevalence of gender change and gender dysphoria reported in the literature was confirmed in this relatively large and homogeneous sample of Iranians with 5α-RD-2 raised as female. Prenatal exposure to testosterone is hypothesized to play a role in the development of gender identity and sexual orientation, but parental attitudes also might be important. Although gender change in individuals with 5α-RD-2 is often attributed to high levels of hostile sexism in some cultures, our findings show this to be associated with benevolent sexism.


Key Words: 5α-Reductase Deficiency Type 2; Psychosexual Outcome; Ambivalent Sexism Inventory; Disorders/Differences of Sex Development; Parental Sexism; Intersex Conditions
INTRODUCTION

5α Reductase deficiency type 2 (5α-RD-2) is an interesting, yet little studied, autosomal recessive endocrine condition belonging to the group of disorders (differences) of sex development (DSD).1 Children with 5α-RD-2 and 46,XY chromosomess have testosterone-secreting testes, but because of a deficiency in the 5α-reductase type 2 isoenzyme causing insufficient dihydrotestosterone production, the testes are mostly undescended and not visible at the birth.2 Dihydrotestosterone is necessary for the development of the normal external genitalia of a male fetus; without it, the external genitalia do not masculinize, resulting in an ambiguous or female-appearing genitalia. In consequence, some children with 46,XY and 5α-RD-2 are raised as female.1,2 The condition is often discovered only after these children enter a virilizing puberty from the testosterone surge brought about by their normal hypothalamic-pituitary-gonadal axis and sex hormone cascade despite the deficient enzyme.3,4 This often includes hirsutism, voice deepening, and increased lead body mass.2 Gonadal removal is sometimes performed in children with 5α-RD-2 raised as female before puberty to prevent virilization if the condition is already identified or in adolescents or adults raised as female who have no desire to change gender despite signs of virilization.5

DSD has challenged the traditional binary concept of the sexes and made room for a novel understanding of sex differences.3,9 If an individual with 5α-RD-2 is raised female, then a situation occurs in which that individual with XY chromosomes whose testosterone serum levels are mostly in the typical male range is designated female at birth and expected to acquire a female gender role. This situation could shed light on the important effect of exposure to sex hormones on psychosexual development. However, studies on the psychosexual outcome of DSD conditions in general and of 5α-RD-2 in particular are rare. This paucity of knowledge is alarming when considering recent reports that 1 in 100 people have some form of DSD.10

A review article, published in 2005, showed that the prevalence of gender dysphoria in people with DSD is highest in those with androgen biosynthesis deficiencies such as 5α-RD-2.1 In this 2005 review on adolescents older than 12 years and adults, gender role changes were reported in 56% to 63% of cases with 5α-RD-2. They usually changed their gender during adolescence or early adulthood and the degree of genital masculinization at birth did not seem to be related to the gender role changes. Moreover, some individuals did not change their gender role but did experience gender dysphoria (2–3%). Many gender changes reported in this review originated from older studies investigating individuals with 5α-RD-2 from the Dominican Republic and the Middle East. These areas have a high prevalence of 5α-RD-2, which is probably related to the fact that consanguineous marriages are relatively common there.

After 2005, many studies described the psychosexual outcomes of people with 5α-RD-2.11–31 Unfortunately, despite the great detail on genetic and hormonal data, assessment of psychosexual parameters remained rather crude. In some cases, gender identity could be inferred only from the fact that those with 5α-RD-2 underwent gonadal removal or other medical treatments. Most studies included very few participants. Of 47 adolescents and adults enrolled in these studies who were designated female at birth, 22 (47%) transitioned to the male gender. Moreover, four participants (8%) were reported to have decreased female identity and high degrees of transgender identity, despite not having officially changed to a male gender. Most participants in these studies underwent gonadal removal after puberty.11,19,20,27,29–34 The large majority of reported cases came to the attention of clinicians after puberty had commenced. Based on the evidence thus far, it is not clear whether and to what extent parental and personal attitudes contribute to the desire to change gender (Table 1).

Thus, we were interested in the potential relation between gender changes in individuals with testosterone synthesis deficiencies and the level of sexism in their families.35,36 Sexism is prejudice or discrimination based on a person’s gender. According to the ambivalent sexism theory, sexism can be hostile (denigrating one sex) and benevolent (idealizing one sex).36 Hostile sexism refers to a paternalistic and antagonistic attitude with the purpose of dominating women and serving to keep women in a narrow and little respected gender role.36 Although benevolent sexism appears to be positive because it refers to women as kind and virtuous, women also are seen as weak, in need of male protection, and good only for few tasks in society. Therefore, it can be as damaging for women’s self-image and place in society as hostile sexism.36 To investigate sexism, the two attitudes should be evaluated.37

For typically developing children, parents have been shown to provide sex-typical environments, such as room décor and clothing, and actively socialize them by encouraging gender-appropriate behavior and discouraging gender-inappropriate behavior.38,39 Moreover, parental reinforcement of sex-typical play correlates with children’s sex-typical play.40 Also, the magnitude of behavioral sex differences is correlated with the level of sexism between societies.35

For those with 5α-RD-2, one can assume that the level of parental sexism strongly affects the likelihood of a person’s decision to change gender. Because sexism is about maintaining each sex in its traditional status and social stereotypes, a family environment that is more sexist would decrease the chance of a gender change. Therefore, independent of the type of sexism, we expected that pressure to remain in one’s assigned gender would be greater in families with higher levels of sexism.

AIMS

The main purpose of this study was to investigate the psychosexual outcome of individuals with 5α-RD-2 in Iran in
Table 1. Gender history, gender identity, and gender role in adolescent and adult 46,XY individuals with 5α-RD-2 reported after 2005 review

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Gender assignment at birth*</th>
<th>Genital appearance at birth†</th>
<th>Gender change</th>
<th>Mean age at study (y)</th>
<th>Lives as</th>
<th>GI</th>
<th>GD</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jong et al,33 2003</td>
<td>Indonesia</td>
<td>1</td>
<td>F</td>
<td>NR</td>
<td>1 FtM</td>
<td>18</td>
<td>1 M</td>
<td>1 M</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bahceci et al,11 2005</td>
<td>Turkey</td>
<td>2</td>
<td>2 F</td>
<td>2 AEG</td>
<td>None</td>
<td>14</td>
<td>2 F</td>
<td>2 M</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Houk et al,19 2005</td>
<td>USA</td>
<td>1</td>
<td>1 F</td>
<td>IV</td>
<td>None</td>
<td>14</td>
<td>1 F</td>
<td>Probably M</td>
<td>Yes, no wish for genital feminization</td>
<td>Psychiatric interview</td>
</tr>
<tr>
<td>Schweizer et al,34 2009</td>
<td>Germany†</td>
<td>3</td>
<td>3 F</td>
<td>3 CM</td>
<td>None</td>
<td>33</td>
<td>3 F</td>
<td>3 M</td>
<td>Different degrees of non-conformity in all 3</td>
<td>Eckloff Gender Identity Questionnaire</td>
</tr>
<tr>
<td>Ismail and Mazen,20 2010</td>
<td>Egypt</td>
<td>3</td>
<td>2 F (1 M)</td>
<td>NR</td>
<td>1 FtM</td>
<td>30.5</td>
<td>1 F, 1 M</td>
<td>2 M</td>
<td>Both were gender dysphoric</td>
<td>Bem Sex Role Inventory</td>
</tr>
<tr>
<td>Zhu et al,31 2014</td>
<td>China</td>
<td>9</td>
<td>8 F (1 M)</td>
<td>4 CM, 4 PSH</td>
<td>8 FtM</td>
<td>17.6</td>
<td>8 M</td>
<td>8 M</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>D’Alberton et al,29 2015</td>
<td>Italy</td>
<td>4</td>
<td>4 F</td>
<td>NR</td>
<td>None</td>
<td>31.5†</td>
<td>4 F</td>
<td>4 F</td>
<td>All feel comfortable in female identity?§</td>
<td>ABCL, WHOQOL-Brief, interview</td>
</tr>
<tr>
<td>Shabir et al,30 2015</td>
<td>India</td>
<td>18</td>
<td>11 F (7 M)</td>
<td>11 CM</td>
<td>8 FtM</td>
<td>17.9</td>
<td>3 F, 8 M</td>
<td>2 F, 9 M</td>
<td>Of the 3 females without gender change, 1 had gender dysphoria</td>
<td>Singh Gender Identity/Dysphoria Questionnaire</td>
</tr>
<tr>
<td>Chan et al,27 2015</td>
<td>Hong Kong</td>
<td>5</td>
<td>3 F (2 M)</td>
<td>3 AEG</td>
<td>None</td>
<td>24</td>
<td>3 F</td>
<td>3 M</td>
<td>All 3 females were tomboys in childhood and required counseling</td>
<td>None</td>
</tr>
<tr>
<td>Bartelloni et al,52 2016</td>
<td>Italy</td>
<td>9</td>
<td>7 F (2 M)</td>
<td>6 CM, 1 AmbGt</td>
<td>1 FtM, (1 MtF)#</td>
<td>21.7</td>
<td>6 F, 1 M</td>
<td>NR</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Deeb et al,63 2016</td>
<td>UAE</td>
<td>5</td>
<td>5 F</td>
<td>4 AmbGt, 1 FP</td>
<td>3 FtM</td>
<td>NR**</td>
<td>3 M, 2 F</td>
<td>4 M, 1 F</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>60</td>
<td>47 F (13 M)</td>
<td>5 AEG, 7 NR, 5 AmbGt, 4 PSH, 1 IV, 1 FP</td>
<td>22 FtM, (1 MtF)</td>
<td>21.6 (12-47)</td>
<td>26 F, 21 M</td>
<td>30 M, 7 F</td>
<td>3 non-F§, 7 NR</td>
<td>WHOQOL-Brief, interview</td>
</tr>
</tbody>
</table>

5α-RD-2 = 5α-reductase deficiency type 2; ABCL = Achenbach-Rescorla Adult Behavior Checklist; AEG = anophthalmia-esophageal-genital; AmbGt = ambiguous genitalia; CM = clitoromegaly; FP = female phenotype with palpable gonads; FtM = female-to-male gender change; GD = gender dysphoria; GI = gender identity; IV = incompletely virilized; MtF = male-to-female gender change; NA = not applicable; NR = not reported; PSH = perineoscrotal hypospadias; UAE = United Arab Emirates; WHOQOL-Brief = World Health Organization Quality of Life, Brief Italian version.

*Only subjects older than 12 years are reported in this table.
†The genital appearance of only those who had been assigned to the female gender is reported in this table.
‡Although these three subjects were living as female, they showed tendencies of increased masculine and transgender identity, decreased feminine identity, and high degrees of uncertainty about gender identity.
§This article reported participants’ age as mean (range).
#One subject had been assigned the male gender at birth and then changed to the female gender in adulthood.
*Participants’ age was not reported; the article only mentioned that they showed signs of virilization, indicating they were adolescents or adults.
greater detail than just presenting the prevalence of gender dysphoria. In addition, we tested the relation between hostile and benevolent sexism and gender change by comparing sexism in those individuals who changed gender vs those who did not.

METHODS

Participants

Participants of this study were part of a larger study on DSD. For this purpose, we analyzed the databases of all hospitals affiliated with the Mashhad University of Medical Sciences (MUMS; Mashhad, Iran), the largest medical center in eastern Iran. Using the International Classification of Diseases, Tenth Revision codes, we searched for all patients registered with various codes for DSD in the MUMS (Table 2). In the absence of performing a routine molecular diagnosis, which is needed for the definite diagnosis of 46,XY DSD and 46,XX DSD, we considered all possible options.

The following exclusion criteria for the selection process: (i) age younger than 5 years, (ii) intellectual disabilities (indicated from the medical charts or during the interview with the psychiatrist), (iii) a genital anomaly and features suggestive of malformation syndromes and (iv) sex chromosome DSD with or without mosaicism, (v) male gender assignment at birth, (vi) missing chromosome karyotype in medical charts, (vii) missing hormonal profile in medical charts, and (viii) missing valid address or phone number of the individual. Figure 1 presents the inclusion and exclusion process and final selection in detail.

Included participants who consented to join the study were seen by a team of endocrinologists from the MUMS. These visits took place at the Endocrinology and Metabolism Research Center of the MUMS and at the time of the weekly meetings of MUMS endocrinologists, which are held to discuss equivocal endocrinology cases. The diagnoses of individuals with 46,XY DSD previously based on hormonal profile and chromosome karyotype were checked using sequencing of the AR gene (the gene that codes for the androgen receptor and is mutated in complete or partial androgen insensitivity syndrome, an important differential diagnosis of 5α-RD-2) and the SRD5A2 gene (the gene that codes for 5α-reductase type 2 isoenzyme). The inclusion criteria for the study were having the 46,XY karyotype, being raised as female, having a confirmed molecular diagnosis of 5α-RD-2, and not fulfilling any of the exclusion criteria listed earlier.

Most parents accompanied their sons or daughters to the clinic. In Iran this is not uncommon. They participated by completing the Ambivalent Sexism Inventory (ASI). Informed written consent was obtained from all participants and their parents. If a participant was younger than 18 years, then informed consent was obtained from parents only. All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the ethics committee of the MUMS and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Materials

Demographics

Demographic data, including age and socioeconomic status (SES), were obtained by a questionnaire. The SES indicators were educational level (highest level attained), head of household’s educational level, marital status, number of first-degree relatives, house ownership, and number of people living together in the current house. SES was calculated using all these parameters according to the method of Islami et al.42

Medical, Sexual, and Family Histories

Gender dysphoria was investigated in all participants using the diagnostic psychiatric interview based on criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) for gender identity disorder.
(GID; data collection for this study took place before the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] was published). Medical, sexual, and family histories were taken from medical records and a semistructured interview by a psychiatrist with an interest in DSD and gender dysphoria. We developed the structure of the interview and are affiliated with the MUMS.

Data on pubertal virilization was obtained in two ways: (i) clinical information at the time of puberty from the medical records if the participants had any and (ii) by asking participants and their parents to describe retrospectively what had occurred during puberty if they had no medical records (voice deepening, extent of pubic hair growth, beard growth, etc). Tanner stage 1 was considered no virilization, Tanner stages 2 and 3 were considered medium virilization, and Tanner stages 4 and 5 were considered high virilization.

We did not use a questionnaire to measure the sexual orientation of participants with 5α-RD-2. The rationale was that, because of the cultural sensitivity of the issue, the answers of participants would be more likely to be honest and trustworthy in an interview in which participants felt safe enough to disclose personal information before responding about their sexuality. The following three questions were asked to all participants who were older than 13 years (because the minimum legal age for marriage for girls in Iran is 13 years; younger girls can be married but require a court’s confirmation): (i) Have you ever had any sexual contact or relationship with a man or with a woman? (ii) Have you ever fantasized about having sex with a man or with a woman? (iii) Have you ever dreamed of having sex with a man or with a woman?

Ambivalent Sexism Inventory
The ASI was administered to participants or their parents to evaluate their level of benevolent and hostile sexism. The ASI consists of two subscales: (i) hostile sexism, which assesses sexist antipathy toward women (eg, “Feminists really want women to have more power than men”) and (ii) benevolent sexism, which assesses sexist positivity toward women (eg, “A good woman should be set on a pedestal by her man”). Each concept is assessed through 11 items, with responses on a six-point scale (0–6) indicating the extent of agreement or disagreement. Therefore, the final score of hostile or benevolent sexism can range from 0 to 55. The Persian version of the ASI has been validated in a study of Iranian college students. The ASI was labeled as a survey about “relationships between men and women.”

Procedure
Participants were invited to the laboratory of the Psychiatric and Behavioral Sciences Research Center in Ibn-e-Sina Psychiatric Hospital for psychological evaluations. Participants and their parents (if they accompanied their children) were interviewed separately with a psychiatrist to obtain a detailed life history. All participants were interviewed at the same location and by the same psychiatrist.

Regarding the ASI, parents of all participants with 5α-RD-2 except those who visited without their parents completed the
questionnaire. They were told that there was no time limit for completing the questionnaires and they should choose the answer they believed best described their position. Each participant answered the questionnaire alone and under similar conditions. Based on who had accompanied the participant with the questionnaire, they should choose the answer they believed best described their position. Each participant was accompanied by their mother, father, older sister, or other family member.

Table 3. Last obtained degree and socioeconomic status

<table>
<thead>
<tr>
<th>Education, n (%)</th>
<th>Dropout</th>
<th>3 (17.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary school</td>
<td>4 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>6 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Master’s degree or higher</td>
<td>4 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17 (100)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Socioeconomic status, n (%)</th>
<th>Low</th>
<th>2 (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium to low</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>9 (45)</td>
<td></td>
</tr>
<tr>
<td>Medium to high</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (100)</td>
<td></td>
</tr>
</tbody>
</table>

The ages of the four individuals who did not want to participate were 19, 21, 22, and 25 years. Their families had a low SES; they were living in populated households, had part-time jobs, and were living in rental houses. None of them were living in a capital city. These four underwent surgery during puberty so that their female-assigned gender at birth would be continued. They expressed their dissatisfaction with these surgeries to us when we invited them to participate (one stated, “I hate the physicians for what they have done to me”).

Diagnosis

As mentioned earlier for the inclusion criteria, all participants were designated female at birth. However, their Prader stage was not documented and thus was unavailable. However, neither the participants (n = 10) who were born when there was no nationwide routinely performed physical examination by a general physician or pediatrician at birth nor those who had this examination had their genitalia described as “atypical.” Three cases in our sample were diagnosed prepubertally, although not at birth: all had inguinal hernia that turned out to be testes. The others were referred to a gynecologist or endocrinologist because of primary amenorrhea. In all cases, chromosome karyotyping had been requested and all five exons of the SRD5A2 gene were sequenced to find mutations for each participant.

Medical History

We distinguished two groups of individuals, those living as male (n = 10) and those living as female (n = 10). This latter group included women with and without genital surgery (see below): FNS (female, no genital surgery but with gonadal removal) described those who continued living in the female role and did not undergo surgery of the external genitals (n = 2, 10%; one underwent gonadal removal at 18 years old and the other at 19); FS (female, with external genital surgery and gonadal removal) described those who continued living in the female role and had the capacity for penile-vaginal intercourse and underwent vaginoplasty and gonadal removal (n = 8, 40%); and MS (male, genital surgery) described those who wished to change or already had changed their gender and need(ed) a phalloplasty (n = 10, 50%). Participants in groups FNS and FS underwent bilateral gonadal removal partly to prevent testicular cancer (Table 4). One participant in the MS group also underwent gonadal removal at the time of diagnosis in an attempt to feminize him. There was no significant difference in mean age among the FNS, FS, and MS groups (F2,17 = 0.574, P = .57) or between the male (mean = 19.30, SD = 7.49) and female (mean = 19.40, SD = 5.75) groups (t18 = −0.33, P = .974).

For medical treatments, all postpubertal subjects in groups FNS and FS had received and were receiving estrogen of participants based on their last obtained degree and SES. The prevalence of SES (χ2 = 5.44, P = .245) and educational level (χ2 = 4.958, P = .175) was compared between the male and female groups. No significant difference was found.

RESULTS

From all registries, 1,267 people with presumed DSD were recruited. Twenty individuals with 5α-RD-2 participated in this study. In addition, four individuals who had been diagnosed with 5α-RD-2 refused to participate in the study.

Demographic Data

The mean age of the participants was 19.5 years (SD = 6.345), with a minimum age of 5 years and a maximum age of 29 years when they participated in this study. Table 3 presents the disparity in participant’s last obtained degree and SES. The prevalence of SES (χ2 = 5.44, P = .245) and educational level (χ2 = 4.958, P = .175) was compared between the male and female groups. No significant difference was found.

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<table>
<thead>
<tr>
<th>Participant number</th>
<th>Group</th>
<th>Family history of DSD</th>
<th>Initial gender assignment</th>
<th>Age (y) at gender change</th>
<th>Age (y) at study</th>
<th>Current gender identity</th>
<th>Extent of virilization at puberty</th>
<th>Hormone treatment</th>
<th>Surgeries requested by participant to date of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FS</td>
<td>+</td>
<td>Female</td>
<td>–</td>
<td>16</td>
<td>Female†</td>
<td>Medium</td>
<td>Conjugated estrogen</td>
<td>GR, CP</td>
</tr>
<tr>
<td>2</td>
<td>FS</td>
<td>–</td>
<td>Female</td>
<td>–</td>
<td>17</td>
<td>Female</td>
<td>High</td>
<td>Conjugated estrogen</td>
<td>GR, CP, LP</td>
</tr>
<tr>
<td>3</td>
<td>MS</td>
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<td>21</td>
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<td>High</td>
<td>Testosterone</td>
<td>Phalloplasty</td>
</tr>
<tr>
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<td>+</td>
<td>Female</td>
<td>–</td>
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<td>Conjugated estrogen + progesterone</td>
<td>GR, CP, VP</td>
</tr>
<tr>
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<td>–</td>
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<td>Conjugated estrogen</td>
<td>GR, CP</td>
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<td>23</td>
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<td>Conjugated estrogen + progesterone</td>
<td>GR</td>
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<tr>
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<td>–</td>
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<td>Testosterone</td>
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<td>High</td>
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<td>GR, CP</td>
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<tr>
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<td>GR, CP</td>
</tr>
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<td>Medium</td>
<td>Testosterone</td>
<td>Phalloplasty</td>
</tr>
</tbody>
</table>

CP = clitoroplasty; DSD = disorders (differences) of sex development; FNS = female, no genital surgery but with gonadal removal; FS = female, genital surgery and gonadal removal; GR = gonadal removal; LP = labioplasty; MS = male, genital surgery; NA = not applicable; VP = vaginoplasty.

*Prepubertal diagnosis.
†Patient underwent bilateral gonadectomy at 2 years of age because of a diagnosis of complete androgen insensitivity syndrome.
‡Participants 1 and 14 had desired to change gender soon after puberty but remained in the gender assigned at birth.
of testosterone received a regime of 250 mg every 10 to 15 days until satisfactory responses were attained.

GID and Gender Dysphoria

Of the 20 participants, 12 (60%) had been diagnosed with GID not otherwise specified (GIDNOS). In the DSM-IV and DSM IV-TR, no GID diagnosis could be given to people with DSD. DSD was an exclusion criterion, even if the symptoms were exactly the same as those in individuals with non-DSD. This was changed in the DSM-5. Ten of 12 participants with GIDNOS transitioned to the male gender. The other 10 participants (50%), including the two with GIDNOS (participants 1 and 14), stayed in the female gender they were assigned at birth.

As mentioned earlier, there were four individuals who were molecularly diagnosed as having 5α-RD-2 but refused to participate in the interview part of the study. When we contacted them, they told us that they were designated female at birth and, when diagnosed with 5α-RD-2 at puberty, had their testes removed and underwent vaginoplasty at their family’s request and not theirs. They were not willing to participate, blaming the physicians for “making” them girls, and were very likely gender dysphoric. However, thus far, they have not returned to the clinic asking for a gender change. Because they blamed the hospital for their unhappy situation, we cannot exclude the possibility that they went elsewhere to have this treatment.

Another subject (participant 10) is noteworthy. He was the only one in our final sample who asked for a gender change against his family’s will. He was raised as female and underwent gonadal removal at 14 years of age—he said against his will. He visited us at 29 years of age and was looking forward to his gender change. At that time, he was completely ostracized by his family. This was an exception because all other families were supportive with whatever the subject had decided to be; for example, they always accompanied their children during their visits.

Except those who underwent a gender change, two other subjects (participants 1 and 14) expressed a desire to change gender immediately after their diagnosis in early puberty. They attended individual and group psychotherapy sessions for individuals with gender dysphoria and were legally allowed to cross-dress (which is legally forbidden for the general female population). After 6 months of psychotherapy, they no longer desired to transition, so they might have resolved their gender dysphoria in one way or another. However, the impact of the expected social stigma on their decision to refrain from a gender change or even the family’s hidden pressure cannot be ruled out.

Except for participants 15, 16, and 17, who were not old enough to decide on their own, all other participants with 5α-RD-2 asked for a gender change. Even in the cases of the prepubertal children (participants 15 and 16), the parents indicated that their children had been very masculine or very gender dysphoric before they had changed gender.

Eight participants with 5α-RD-2 did not have visible signs of virilization (no or medium pubertal virilization) and nine had visible signs of virilization (high pubertal virilization). There was no significant difference in gender dysphoria between participants with and those without visible signs of virilization ($\chi^2 = 2.286, P = .131$).

Sexual Orientation

Fifty percent of participants were single (five living as female and five living as male), 20% were married (three living as female and one living as male), and 15% were engaged (one living as female and two living as male; Table 5). For the remaining 15%, the relationship status or any sexuality-related variables were not applicable because of their age. As presented in Table 5, 55% of participants had experienced at least one sexual relationship (20% with a male partner, 15% with a female partner, and 20% with a male and a female partner).

Of those who transitioned from female to male and were older than 13 years (n = 8), only one (participant 8) had no sexual experience before the sex change; the others had been sexually active before their gender transition (three had sexual contact only with women and four had sexual contact with men and women). However, in their sexual fantasies, only one case (15%) was ambiphilic, and all the rest (n = 7, 85%) were exclusively gynephilic and had no sexual fantasy about men. In addition, one participant (15%) reported having dreamed at least once of a sex act with a male partner, but also reported sex dreams with a female partner. All the rest had exclusive gynephilic dreams.

When comparing the experiences of sexual contacts ($\chi^2 = 14, P = .007$), sexual fantasies ($\chi^2 = 10.833, P = .020$), and sexual dreams ($\chi^2 = 10.705, P = .030$) between those who made a gender transition and those who did not, the transitioned group reported a significantly stronger gynephilic orientation than those who lived as female. All those who had transitioned to the male gender asserted that their sexual fantasies and dreams had not changed during or after the transition.

Interestingly, 40% of female participants who lived in the female gender had gynephilic fantasies, and 50% of them had gynephilic dreams, irrespective of their marital status. We also investigated these participants for whether gynephilic sexual contacts ($\chi^2 = 6.631, P = .085$), fantasies ($\chi^2 = 7.802, P = .05$), and dreams ($\chi^2 = 7.338, P = .062$) differed among.
them for various levels of virilization: those with more virilization more often reported gynephilic sexual fantasies (77%) and dreams (66%) than those with less virilization (12.5% for fantasies and dreams), although the difference was significant only for fantasies.

Ambivalent Sexism Inventory

The mean ASI total, hostile sexism, and benevolent sexism scores in this sample were 68.6 (SD = 10), 34.4 (6.92), and 34.16 (7.18), respectively. The ASI score of this sample was significantly higher than the comparison score of college students (ASI score = 53.4, mean difference = 15, 95% CI = 10.51–19.55, t20 = 6.934, P < .001). This also was true for hostile sexism scores (t20 = 3.910, P = .001, mean difference = 5.552, 95% CI = 2.59–8.51) and benevolent sexism scores (t20 = 5.689, P < .001, mean difference = 9.476, 95% CI = 6.00–12.95).

For parents whose daughter changed gender compared with those whose daughter stayed in her birth-assigned gender, there was no difference in ASI hostile sexism (t16 = −0.256, P = .794) and total sexism (t16 = −1.658, P = .117) scores, but there was a difference in the benevolent sexism score (t16 = −2.125, P = .049; Table 6).

Table 5. Sexual orientation

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Current age</th>
<th>Lives as</th>
<th>Relationship status</th>
<th>Have you ever had any form of sexual contact with</th>
<th>Have you ever fantasized about having any form of sexual contact with</th>
<th>Have you ever dreamed of having any form of sexual contact with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
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<td>Women</td>
<td>Men</td>
</tr>
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NA = not applicable.

*Prepubertal diagnosis.

DISCUSSION

Different factors can contribute to the decision to change gender in an individual with DSD. In addition to biological factors such as a syndrome, syndrome severity, initial gender assignment, medical treatment, and prenatal testosterone exposure, cultural factors can play a role. Half of our participants (10 of 20) had undergone medical procedures to transition to the male gender. This is in line with the prevalence of gender changes (and gender dysphoria) in 110 persons with 5α-RD-2 who were reported in the 2005 review. However, our prevalence was lower than in studies published after the 2005 review. It is interesting that the numbers of gender changes in Western-educated industrialized rich democratic (WEIRD) countries seem to be smaller than in non-WEIRD countries and that even individuals raised as female with a late diagnosis are more satisfied with their female gender than those living in non-WEIRD societies. The higher rate of gender changes in non-WEIRD countries could be related to the rigidity of gender roles. Although classic Islamic law explicitly recognizes four genders, Iran is a highly binary society. In such a binary society, all individuals are forced into one of two social gender roles, whereas in more flexible societies, persons with DSD can experience and express more gender fluidity.
The greater social privileges of men vs women can serve as a motive to change gender from female to male.47 Iran has an emerging economy and far from gender equality. In 2014 it was ranked 137 of 142 countries by the World Economic Forum using the Gender Gap Index.48 In such countries, it can be socially advantageous for individuals with 46,XY 5α-RD-2 raised as female to change gender. However, gender dysphoria and a desire to change gender can develop very young in life, long before children perceive social discrimination against women. Also, it is not clear whether the social privileges of men can surpass the social stigma and probable ostracism of being a transman in a traditional society in which the choice of gender change is socially costly and normatively unacceptable.

We found significantly higher scores on sexism in our sample than in our comparison group, which could be explained in part by the fact that college students are less traditional. However, a child with DSD often comes from a consanguineous marriage and consanguinity can occur more often in arranged marriages. Such marriages are more likely in families with traditional ideologies regarding gender roles. In addition, parents of children with DSD might be more focused on the male and female social roles than other parents because their thinking about gender roles might have become emotionally loaded and complicated since the diagnosis of their child. Concerns about their child’s gender might amplify their already existing traditional views and sexist aspects of Iran’s legal and cultural atmosphere.49

Irrespective of the origins of the parental attitudes, the offspring’s decision to change gender was related to a significantly higher level of benevolent sexism. Because there was no difference in SES between these two groups, the difference in benevolent sexism is not explained by differences in SES. One can interpret this as an attempt of parents (or the family as a whole) to keep the individual with 5α-RD-2 in her birth-assigned female gender in a “nice” and not hostile way. However, this attitude might have been experienced as suffocating by the child and facilitated gender changes. Clearly, more studies are necessary for further explanations.

Sixteen participants experienced the testosterone surge at puberty, resulting in a virilizing puberty that was highly (n = 9) or moderately (n = 7) visible (Table 3). There was no significant difference in the likelihood of gender dysphoria between the two groups and one participant with 5α-RD-2 who was diagnosed with GIDNOS had even undergone gonadal removal at 2 years of age. This finding is in line with studies suggesting that prenatal androgens rather than androgen levels play a crucial role in atypical sexual differentiation later in life.50

In this study, most participants had increased levels of gynephilia and ambiphilia. This is in concordance with studies on people with congenital adrenal hyperplasia whose sexual orientation has been reported to diverge from the androphilia of matched female controls51 and individuals with complete androgen insensitivity syndrome who have been mostly described as completely androphilic.52 Our findings support the results of these studies, suggesting a substantial effect of prenatal androgens on sexual orientation.53 Not surprisingly, those who had changed gender showed significantly more gynephilia—in their contacts, fantasies, and dreams—that those who had not. This makes it likely that prenatal androgens contribute to male gender identity and gynephilia.54

Considering the legal and cultural discrimination against individuals with a non-heterosexual orientation in Iran, one wonders whether those who changed gender tried to avoid the stigma and legal consequences of their gynephilia55 rather than gender dysphoria. However, this explanation seems unlikely. First of all, most of those who changed gender had their sexual contacts with women before their gender transition. In fact, being regarded as a female in a country where men and women are forcefully segregated facilitates finding and having relationships with women.56 Transition to the male gender strongly decreases the opportunity of having access to potential sexual partners. Second, same-sex relationships are not a very rare phenomenon in Iran. According to a recent report of the Iranian Ministry of Education on 141,555 students, 70.4% reported having a heterosexual relationship and 17.5% (n = 24,889) reported having same-sex relationships.61 Although this does not downplay the difficulties Iranian homosexuals are facing, it does show that same-sex relationships are rather prevalent and possible without any need to change gender.

Gynephilic sexual behavior and dreams were, similar to gender dysphoria and dissimilar to fantasies, not significantly different between individuals with various degrees of pubertal virilization. This suggests that pubertal androgens did not play a major role in the sexual orientation of these participants.
Limitations

The sample was fairly large compared with previous studies, all with molecularly confirmed diagnoses, and it had the advantage of being homogeneous for country of origin and treatment center. However, because of the rarity of this condition, the sample was still small enough to decrease statistical power.

The participants’ gender identity was investigated in an interview with a psychiatrist so that they could express themselves in a more elaborated way rather than being restricted to predetermined, limited choices. Non-qualitative approaches, particularly in societies in which gender and sexual orientation are sensitive topics, could lead to the loss of important data. For example, it has been shown that despite living in the female role, persons with DSD had tendencies toward increased male and transgender identity, decreased female identity, and high degrees of uncertainty regarding their gender identity. Most of the current available questionnaires on female and male identity might not be sufficient if a study focused on gender identity is warranted—particularly DSD—because instruments for measuring non-binary gender identities hardly exist. During a face-to-face interview, the interviewee can ask a wider range of open questions on gender identity.

Lack of documentation on the Prader stages of participants with 5α-RD-2 at birth or detailed information about the extent of virilization at the time of diagnosis limited our ability to investigate the association between the psychosexual outcomes and the prenatal effects of testosterone.

For comparing the sexism scores, using a matched control group (educationally and economically) of parents would have been more elegant. However, was not possible within the scope of our study.

Future studies would benefit from the use of instruments that measure multiple dimensions of gender dysphoria, instead of using a variable such as the presence or absence of gender change or fulfilling GIDNOS criteria, although reports on non-binary gender identities or gender dysphoria in cultures such as Iran’s might not be currently likely. Therefore, we believe that our approach offered a good opportunity to gather relevant information, given the current situation.

The cross-sectional design of our study made it necessary to gather some information retrospectively through medical records and interviews with our participants with 5α-RD-2 and their family members, which could have caused bias. Long-term prospective cohort studies can overcome this limitation.

CONCLUSION

Virilized and non-virilized female-raised individuals with 5α-RD-2 are exposed to prenatal androgens. Therefore, the absence of differences in gender change between virilized and non-virilized individuals suggests prenatal rather than postnatal androgen effects on the development of gender identity. Growing up in families who define the female role in a narrow way, even if this narrow female role is viewed as positive, could serve as an extra force in the choice of changing gender. The high occurrence of gynephilic or ambiphilic sexual fantasies and dreams suggest the influence of prenatal exposure to testosterone in the development of sexual orientation.

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