

## Research Article

# Analysis of Gender Assignment and Gender Transition in Chinese Patients with Disorders of Sex Development

Zhiwan Liu<sup>#</sup>, Hong Gao<sup>#</sup>, Di Zhou<sup>#</sup>, Zheyuan Hu, Wenjun Zhang, Yaozhong Zhao, Xiaohai Zhu<sup>#</sup>, and Lie Zhu<sup>\*</sup>

Department of Plastic and Reconstructive Surgery, Changzheng Hospital, Navy Medical University, China

<sup>#</sup>These authors contributed equally to this manuscript

**\*Corresponding author**

Lie Zhu, Department of Plastic and Reconstructive Surgery, Changzheng Hospital, Navy Medical University, Mailing Address: No.415 Fengyang Road, Huangpu District, 200003, Shanghai, China

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**Keywords**

- Disorders of Sex Development
- Sex assignment
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**Abstract**

**Background:** For individuals with DSD, the decision of gender assignment at birth is a challenging one and the incidence of gender dysphoria in adulthood is much higher than that in the general population.

**Aim:** Our goal is to provide strategies for gender assignment at birth for individuals with DSD and investigate the underlying reasons for gender transition in DSD patients.

**Methods:** Conducting a retrospective clinical case analysis of DSD patients admitted to our department from 2000 to 2020, with a focus on analyzing the reasons for gender reassignment among these patients.

**Results:** In 91 cases of 46, XY DSD, 71 were raised as females and 20 as males. Among them, gender transition occurred in 18 cases, with 17 female-to-male (FTM) transitions and one male-to-female (MTF) transition. In the case of 53 patients with 46, XX DSD, there were 39 who were raised as females and 14 as males. After diagnosis and treatment, a total of nine cases underwent gender transition, including seven FTM transitions and two MTF transitions.

**Clinical Implications:** The choice of gender assignment at birth significantly impacts the occurrence of future gender dysphoria, emphasizing the importance of increased attention to individuals with DSD who experience gender dysphoria.

**Strengths and Limitations:** This study provides a detailed analysis of the reasons for gender transition in individuals with DSD and offers some references for gender assignment at birth based on previous literature. However, the major limitation of this study is the lack of specific etiology for DSD patients who undergo gender transition.

**Conclusion:** For children with abnormal external genitalia at birth, it is recommended that chromosome karyotype analysis and gene detection be performed immediately. A proper upbringing regarding gender can greatly reduce the occurrence of gender anxiety in patients and the resulting suffering.

**ABBREVIATIONS**

DSD: Disorders of Sex Development; CAIS: Complete Androgen Insensitivity Syndrome; PAIS: Partial Androgen Insensitivity Syndrome; FTM: Female-to-Male; MTF: Male-to-Female; CAH: Congenital Adrenocortical Hyperplasia

**BACKGROUND**

Disorders of sex development (DSD) refer to a congenital anomaly characterized by abnormal development of chromosomes, gonads, and/or external genitalia. In the past, such conditions were referred to as Intersex or hermaphroditism. DSD has complex etiology and presents with a variety of clinical manifestations. In 2006, the Lawson-Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology

classified DSD into three major categories: 46,XY DSD, 46,XX DSD, and sex chromosome DSD [1]. About 80% of DSD patients have a karyotype of XY, 10-15% are XX, and the rest are sex chromosome aneuploidies or mosaics [2]. 46, XY DSD is a congenital disorder characterized by an inconsistent phenotype and chromosomal sex with a 46, XY karyotype. It encompasses a range of conditions caused by genetic variations, alterations in hormone secretion, or abnormal response of target organs to testicular hormones. These abnormalities can affect the development of male reproductive organs in male fetuses, resulting in varying degrees of masculinization deficiency or even complete manifestation as female [1,3-5]. There are various subtypes of 46, XY DSD, such as gonadal dysgenesis, androgen insensitivity syndrome, 5 $\alpha$ -reductase deficiency, 17 $\beta$ -hydroxysteroid dehydrogenase deficiency, and persistent Müllerian duct syndrome, among

others. 46, XX DSD is primarily caused by exposure to excessive androgens during fetal or postpartum periods, which can originate from the fetus, placenta, or mother. Approximately 95% of 46, XX DSD cases are attributed to congenital adrenocortical hyperplasia (CAH), a condition resulting from enzyme deficiencies that impact the hormone synthesis pathway [6-8].

Gender assignment is typically based on the external genitalia of a new infant. When a newborn presents with atypical genitalia, correct gender assignment is one of the most difficult decisions for clinicians. When gender is determined, the assigned gender and gender identity should be consistent; otherwise, it can lead to gender dissatisfaction and gender anxiety in patients, causing serious physical and mental harm to them and their families [9]. Sexual psychosocial development is a complex process influenced by various factors, such as exposure to androgens, sex chromosome genes, social environment, and family beliefs [10]. One of the most crucial aspects of psychosexual development is gender identity, which refers to an individual's inherent self-awareness as male, female, or another gender [11]. Many factors need to be considered in gender assignment, such as patients' gender cognition, parental gender preference, genital development, sociocultural factors, religious beliefs [12]. Sex dissatisfaction was found to occur more frequently in DSD patients compared to the general population. Incorrect gender assignment will bring great physical and psychological pain to patients and their families [13].

Thus, this study examined the assignment of gender at birth, cases of gender transition during adolescence or adulthood, and the analysis of reasons for gender transition in DSD patients treated at our department over the past 20 years. The objective is to provide a foundation for determining the assigned gender at birth for DSD patients.

## SUBJECTS AND METHODS

### Subjects

From January 2000 to January 2021, a total of 149 patients diagnosed with DSD received inpatient treatment at the Department of Plastic Surgery, Shanghai Changzheng Hospital. Among them, there were 91 cases (61%) of 46, XY DSD patients, 53 cases (36%) of 46, XX DSD patients, and 5 cases (3%) of sex chromosome DSD. Inclusion criteria include: (1) ambiguous external genitalia; (3) bilateral inguinal hernia in females; (4) delayed or incomplete puberty; (5) masculinization of female during puberty; (6) breast development in male during puberty; (7) cryptorchidism with or without hypospadias. Exclusion criteria: (1) transsexual patients; (2) those with missing clinical data.

### Methods

A retrospective analysis of clinical cases was conducted on 149 patients with DSD who were admitted to our department between 2000 and 2020, see Table 1. This analysis includes (1) the distribution of assigned gender at birth; (2) situations

**Table 1:** Gender distribution and gender transition among individuals with DSD

		46, XY DSD(n)	46, XX DSD(n)	sex chromosome DSD(n)
raising sex	male	20	14	3
	female	71	39	2
gender transition	FTM	17	7	0
	MTF	1	2	0

involving gender transition; and (3) the reasons for undergoing gender transition.

### Statistical Analysis

Use SPSS 26.0 statistical analysis software to organize, summarize, and analyze data. Descriptive statistics will be used for categorical data represented as n (%), while mean or median will represent quantitative data.

## RESULTS

### Gender Assignment at Birth and Reasons for Presentation in Patients with 46, XY DSD

Out of 91 cases of 46, XY DSD patients, 71 (78%) were assigned female and 20 (22%) were assigned male. Among the 71 patients who were raised as females, 55 cases (78%) sought medical attention for primary amenorrhea during adolescence, while 14 cases (20%) presented with masculinization during adolescence. The remaining two cases (2%) sought medical attention due to genital malformation and painful urination. In 14 (70%) out of the 20 patients who were assigned male at birth, they sought medical attention due to insufficient adolescent masculinization or adolescent male feminization/gynecomastia, while 6 patients (30%) sought medical attention for perineal malformations.

### Gender Transition Status and Reasons for Gender Transition in Patients with 46, XY DSD

A total of 18 patients underwent gender transition during adolescence or adulthood after diagnosis and treatment, including 17 FTM transitions and 1 MTF transition. Among the 17 FTM patients, 4 requested gender transition due to their psychological identification as male after puberty, 9 desired to transition to male due to masculinization during adolescence, and 4 were diagnosed with 46, XY DSD after gradual masculinization in prepuberty at the request of their parents for a male transition.

A patient who was assigned male at birth is requesting to transition to female due to underdeveloped male secondary sexual characteristics and breast development during puberty.

### Gender Assignment at Birth and Reasons for Presentation in Patients with 46, XX DSD

Out of 53 cases of 46, XX DSD patients, 39 (74%) were assigned female and 14 (26%) were assigned male. During adolescence, 16 out of the 39 patients (41%) experienced primary amenorrhea at birth, while 9 (23%) had clitoral hypertrophy and 7 (18%) showed signs of masculinization. The remaining 7 (18%) experienced recurrent lower abdominal pain and perineal

malformation during puberty. Fourteen patients assigned male at birth mainly presented with adolescent menstruation, periodic lower abdominal pain during puberty, breast development in adolescence, perineal malformation, abdominal mass, and absence of male secondary sexual characteristics during puberty.

### Gender Transition Status and Reasons for Gender Transition in Patients with 46, XX DSD

After diagnosis and treatment, a total of 9 cases (17%) underwent gender transition, with 7 cases (78%) transitioning from female to male and 2 cases (22%) transitioning from male to female. Among the 7 FTM patients, 6 patients were converted to male due to clitoris hypertrophy (3~5cm) and male psychological gender; One case was diagnosed as 46, XX DSD due to perineal malformation and high psychological pressure, and the individual requested a gender transition to male. Two MTF patients were converted to females due to periodic abdominal pain during puberty, inadequate development of male secondary sexual characteristics, and lack of development of male secondary sexual characteristics in adolescence.

## DISCUSSION

In our study, a total of 149 patients with DSD were included, comprising 112 individuals (75%) assigned female at birth and 37 individuals (25%) assigned male at birth. Among them, there were 27 cases (18%) who underwent gender transition later in life, including 24 cases (89%) transitioning from female to male and 3 cases (11%) transitioning from male to female. Reviewing the medical history, it is observed that most patients who undergo gender transition do so due to a severe mismatch between their psychological gender identity and external genital development. These individuals experience significant psychological distress and feelings of inadequacy regarding their assigned gender, ultimately seeking relief through gender reassignment surgery in order to alleviate this gender dysphoria.

DSD patients have diverse clinical manifestations, ranging from normal female genitalia, clitoral hypertrophy, micropenis, and hypospadias, to complete male genitalia. According to different clinical phenotypes, there may also be variations in the assigned gender at birth. In the past few decades, there has been a long-standing consensus among people regarding sexual psychological differentiation, sex and gender, as well as gender assignment in various types of external reproductive organs [9,14-20]. Sexual psychosocial development is influenced by various factors, including exposure to androgens, sex chromosome genes, brain structure, the social environment, and the family environment. Sexual psychosocial development encompasses three domains: gender identity, gender roles (also known as gender behavior), and sexual orientation. In general, there is a certain correlation between sexual psychological development and the gender of upbringing, but this is not a rule [21]. Prenatal exposure to sex hormones and the degree of masculinization of external genitalia, but the specific extent of their impact is still unknown. Gender identity refers to a person's

conscious or unconscious recognition of the gender they belong to. The critical age for developing gender identity is between 18 and 36 months. Gender identity dysphoria occurs when an individual believes that their gender identity is incorrect. Gender dissatisfaction refers to the discontent with one's assigned gender at birth. Compared to the general population, individuals with DSD experience a higher frequency of gender dissatisfaction and gender identity dysphoria [10,11,13,22]. When determining the gender of a newborn, various factors need to be taken into consideration, including the patient's gender identity, parental gender preferences, genital development, social and cultural influences, and religious beliefs.

Guidelines recommend that 46, XX CAH patients be raised as females, except for those who have been raised as males due to severe masculinization or identify themselves as male. It makes sense because these patients have the ability to conceive and give birth, and even in adulthood, the likelihood of experiencing gender dysphoria is relatively low [23]. There are three unavoidable issues for 46, XX CAH male patients throughout their lives: 1. Ultimately shorter stature in adulthood; 2. The need for surgeries to remove the ovaries and uterus in order to prevent feminization, breast development, and urethral bleeding (menstrual cycle); 3. Infertility [24]. There is already a wealth of research indicating that individuals with CAH who are raised as males have a higher incidence of gender dysphoria compared to those raised as females [18,25-30]. Therefore, the proportion of CAH patients who were assigned male at birth and choose to transition to female is higher than that of CAH female patients.

Due to prenatal and/or postnatal exposure to androgens, approximately 70% of patients with 5 $\alpha$ -reductase deficiency develop a male gender identity during their growth process and undergo a change in gender behavior during adolescence or early adulthood [31]. It is not uncommon for female caregivers of patients with 5 $\alpha$ -reductase deficiency syndrome to undergo a gender transition during adolescence. McGinley et al., reported that out of 18 patients with 5 $\alpha$ -reductase deficiency, 17 chose to transition from female to male during adolescence [32]. Deeb et al., reported a family with 46, XY DSD caused by mutations in the SRD5A2 gene, where six individuals with 5 $\alpha$ -reductase deficiency were raised as females. Among them, one individual transitioned to male at the age of two, while the other five experienced masculinization during puberty. Out of these patients, three opted for gender reassignment, while only two remained identified as females [33]. Amaral et al., conducted a retrospective analysis on DSD patients aged 18 and above, among whom 13 out of 25 cases with 5 $\alpha$ -reductase deficiency syndrome transitioned to the male social gender [34]. Joseph et al., reported on 12 patients with 5 $\alpha$ -reductase deficiency, of whom 11 were raised as females. Among these 11 individuals, 10 opted for gender transition to become males [35]. In 5 $\alpha$ -reductase deficiency, gender transition (FTM) is encouraged and supported because these patients who undergo gender reassignment have well-developed psychosis and external genitalia. Wisniewski et al. investigated the psychological and sexual well-being of 14 female

patients with CAIS, all of whom expressed satisfaction with being raised as females and had no desire to transition genders [36]. The incidence of gender anxiety among CAIS female patients is extremely low; therefore, there is no dispute regarding the viewpoint that CAIS patients should be raised as females. A systematic review conducted by Babu et al. on gender identity disorders in individuals with DSD found that the prevalence of gender dysphoria was 12% among female patients with partial androgen insensitivity syndrome (PAIS), and 25% among male patients, although there was no statistically significant difference between the two groups. Therefore, the choice of assigned gender for children with PAIS is currently uncertain [22].

In this study, out of 53 patients with 46, XX DSD, 9 underwent gender transition, including 7 females transitioning to males and 2 males transitioning to females. The main reasons for gender conversion in seven FTM patients were clitoral hypertrophy (3-5cm) and a psychological desire to transition to male. These patients, although raised as females after birth, have undergone severe masculinization of the external genitalia exposure to androgen stimulation. Therefore, their psychological gender is male. Long-term gender identity incongruent with assigned gender in upbringing leads to gender dysphoria and compromises the patient's mental and physical well-being, ultimately driving them to seek surgical intervention for gender transition as a means of alleviating their anxiety. In contrast, there have been no reported cases of gender transition among female patients with external reproductive organs that fall between those of typical females and typical males. Among the 91 patients with 46, XY DSD, 18 individuals underwent gender transition, including 17 females transitioning to males and one male transitioning to female. Among the 17 FTM patients, the main reasons for gender transition were identified as having a male psychological gender identity after puberty, experiencing masculinization during adolescence, and undergoing gradual masculinization in pre-adolescence. These patients are all appeared female external genitalia at birth, but during the process of growth and development, their external reproductive organs gradually masculinized and their gender identity shifted towards male. As a result, they or their parents eventually requested a gender transition.

## CONCLUSIONS

For patients with 46, XX DSD, it is recommended to be raised as female. However, for those with severe masculinization of external genitalia male gender identity consistent with their assigned sex at birth, they should continue to be raised as male. Due to the numerous subtypes of 46, XY DSD and their similar clinical presentations at birth, it is often challenging to obtain a definitive diagnosis through physical examination, hormone testing, imaging findings, or chromosomal karyotype. Therefore, we recommend conducting genetic testing prior to assigning the gender of 46, XY DSD patients during their upbringing. If it is CAIS, then choose the female gender for upbringing; if it is 5 $\alpha$ -reductase deficiency, then choose the male gender for upbringing.

## AVAILABILITY OF DATA AND MATERIALS

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

## Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Authors' Contributions

Xiaohai Zhu and Lie Zhu supervised the entire study, including the procedures, conception, design and completion. Zhiwan Liu, Hong Gao and Di Zhou contributed to the data analysis and drafted the article. Zheyuan Hu, Wenjun Zhang and Yaozhong Zhao participated in the interpretation of the study data and in revisions to the article. All authors contributed to the article and approved the submitted version.

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