

Primary Amenorrhea in a Patient With 46, XY Disorder of Sex Development: A Case Report

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ABSTRACT

Introduction: 46,XY gonadal dysgenesis is a rare entity within disorders of sexual development. This case is unique because it describes a patient who underwent irreversible sex assignment surgeries during childhood without histological confirmation, which contrasts with current recommendations. Its contribution to the literature lies in highlighting the diagnostic and psychosocial challenges of these conditions, even when molecular studies yield negative results.

Case presentation: A 19-year-old woman, student, with a history of bilateral orchiectomy and penectomy at 2 years of age. She presented with primary amenorrhea and absence of secondary sexual characteristics. Physical examination revealed severe hypogonadism, hypergonadotropism, absence of uterus and adnexa, and a 17% reduction in bone mineral density. Karyotype confirmed 46,XY with a positive SRY gene, and a panel of 53 genes associated with disorders of sexual development was negative.

Interventions and outcomes: Management included hormone replacement therapy with estradiol and medroxyprogesterone, calcium and vitamin D supplementation, and psychiatric treatment with escitalopram for depression and anxiety. As part of her gender affirmation process, she underwent breast implants with good postoperative evolution. She is currently under multidisciplinary follow-up with subjective improvement in mood and clinical stability.

Conclusions: The main lessons from this case are the importance of avoiding early irreversible surgeries, recognizing the limitations of molecular studies, ensuring a comprehensive approach that includes psychosocial support, and guaranteeing the active participation of the patient in therapeutic decisions to optimize health and quality of life in 46,XY disorders of sexual development.

KEYWORDS: gonadal dysgenesis, 46,XY disorder of sex development, primary amenorrhea, hormone replacement therapy, estrogens, psychosocial support, molecular diagnosis.

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INTRODUCTION

Differences/Disorders of Sex Development (DSD) are a heterogeneous group of congenital conditions resulting in a discordance between an individual’s sex chromosomes, gonads, and/or anatomical sex. Newborns with genitalia that are not typically male or female in appearance, or that appear

discordant with their chromosomal sex, are classified as having a Difference (or Disorder) of Sex Development (DSD). DSDs with genital ambiguity severe enough to prompt medical evaluation occur in approximately 1 in every 1,000 to 4,500 live births.^{1 2}

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According to the 2006 Chicago Consensus, DSDs are divided into three categories: 46,XX DSD, 46,XY DSD, and sex chromosome DSD—a classification widely recognized in clinical practice. Gonadal differentiation and development is a complex process regulated by the interaction of genetic networks and hormonal signaling. The 46,XY DSD group encompasses multiple etiologies, including disorders of testicular development and defects in androgen synthesis or action, leading to varying degrees of undervirilization. In 46,XY individuals, when testes develop, they secrete AMH, which inhibits the development of Müllerian-derived structures (uterus, fallopian tubes, and upper vagina), explaining uterine absence. Ultrasound is the main imaging method for assessing the presence of gonads and Müllerian structures and constitutes the first diagnostic step in 46,XY DSD due to its convenience and cost-effectiveness. These disorders are classified into two categories based on the presence or absence of the uterus on ultrasound.^{3,9}

Diagnosing 46,XY disorders of sex development remains a clinical challenge due to their genetic and phenotypic heterogeneity. Although clinical, endocrinological, and imaging evaluations are the foundation of initial assessment, they are often insufficient to establish an etiologic diagnosis. In this context, modern genomic technologies such as exome and whole-genome sequencing have significantly improved diagnostic yield, enabling the identification of pathogenic variants previously undetectable by conventional methods. Nevertheless, despite these advances, the rate of confirmed molecular diagnosis in 46,XY DSD remains below 50%, reflecting the genetic complexity of these conditions. Early diagnosis not only guides medical and surgical decisions but is also essential to address psychosocial and fertility implications. Therefore, a multidisciplinary approach integrating clinical, genetic, and specialized counseling is recommended.⁴

We present the case of a patient with 46,XY DSD and gonadal dysgenesis, whose diagnosis was established due to primary amenorrhea and absence of secondary sexual characteristics, illustrating the clinical and therapeutic challenges of this condition.

The objective of this report is to describe a case of 46,XY gonadal dysgenesis managed through an integral clinical, endocrinological, and psychosocial approach, highlighting the ethical challenges and implications of early surgical interventions, as well as their long-term impact on quality of life.

CASE REPORT

This is the case of a 19-year-old female, student, with a sedentary lifestyle and a hypocaloric, low-protein diet. At birth, she presented with ambiguous genitalia, with documentation of testes and a penis. During the neonatal period, diagnostic studies were performed, though their results are no longer available. At 2 years of age, she

underwent bilateral orchiectomy and penectomy, a decision made solely for female sex assignment purposes and without prior gonadal biopsy. The family lost the pathology reports; thus, no histological confirmation of the resected gonads is available. There was no family history of disorders of sex development or relevant endocrine diseases.

The patient presented to the Gynecology Department for evaluation of primary amenorrhea and absence of secondary sexual characteristics. She reported that she first noticed the absence of menstruation at age 14 but did not seek medical attention until age 16, when the lack of pubertal changes became more evident. Genetic testing confirmed a 46,XY karyotype with the presence of the SRY gene (Figure 1), establishing the diagnosis of gonadal dysgenesis. Additionally, a molecular panel of 53 genes associated with DSD yielded negative results, with no identifiable pathogenic variants.

On physical examination, height was 160 cm, weight 61 kg, body mass index 24 kg/m², and blood pressure 110/70 mmHg. Normal body hair distribution was observed, with absence of axillary hair, Tanner stage I breast development with incipient breast buds, and external genitalia with sparse pubic hair, poorly differentiated labia majora and minora, an infantile vaginal introitus, and an intact hymen; therefore, speculum or bimanual examination was not performed. A short perineum and a hypertrophic, hyperpigmented clitoris were also noted (Figure 2).

Laboratory tests revealed hypergonadotropic hypogonadism with LH 22 mIU/mL and FSH 72 mIU/mL, associated with severe hypogonadism: total testosterone 0.025 ng/mL, estradiol 5 pg/mL, and progesterone 0.08 ng/mL; anti-Müllerian hormone was undetectable (<0.07 ng/mL). Tumor markers (AFP, β -hCG, and LDH) were negative. Other biochemical parameters, including thyroid profile, glucose, and HbA1c, were within normal ranges. Pelvic computed tomography demonstrated absence of uterus and adnexa. Bone densitometry of the lumbar spine and hip showed an average 17% reduction in bone mineral density.

Endocrinology prescribed hormone replacement therapy with estradiol valerate (Primogyn) in a progressive pubertal induction scheme up to 2 mg/day, followed by an estrogen-progestin combination of medroxyprogesterone/estradiol (Cyclofemina) containing 5 mg medroxyprogesterone and 2 mg estradiol monthly, aiming to achieve adequate sex hormone levels, induce secondary sexual characteristics, and prevent long-term complications. Calcium supplementation (1 g/day) and vitamin D3 (800 IU/day) were added for bone protection. Psychiatric management included escitalopram 10 mg/day for depression and anxiety, with good adherence and tolerance. Since initiating treatment, the patient has shown decreased pubic hair, mild breast tension without significant glandular volume increase, and subjective improvement in mood.

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Psychosocially, she reported difficulties in interpersonal and academic relationships, resulting in significant emotional distress. She was evaluated by Psychology and Psychiatry, who confirmed diagnoses of depression and anxiety, initiating psychotherapy and pharmacologic treatment. As part of her gender affirmation process, she requested breast augmentation, which was performed by the Plastic Surgery team using implants, with satisfactory postoperative evolution. She is currently planning genital reconstruction surgery after an informed consent process and interdisciplinary counseling.

The patient continues follow-up with Gynecology, Endocrinology, Psychiatry, and Plastic Surgery under a long-term monitoring plan including periodic bone densitometry, cardiovascular and metabolic assessments, lipid and glucose control, and continuous evaluation of hormone replacement therapy. No adverse effects have been reported. Follow-up includes semiannual laboratory and clinical assessments, with reevaluation of bone density every 18 months and hormonal adjustment according to response. This schedule aims to ensure endocrine stability, bone health, and long-term emotional well-being.

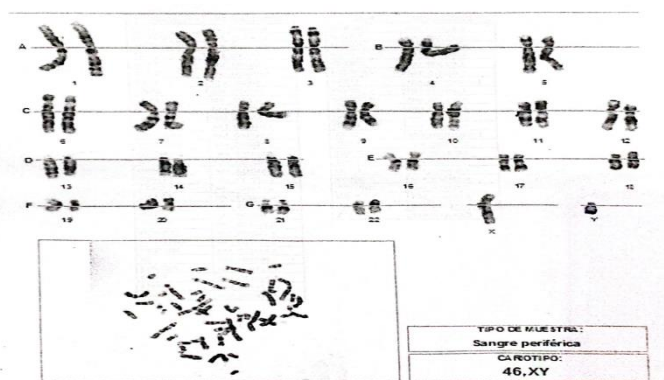


Figure 1. Karyotype obtained from a peripheral blood sample showing a 46,XY chromosomal constitution, consistent with gonadal dysgenesis.

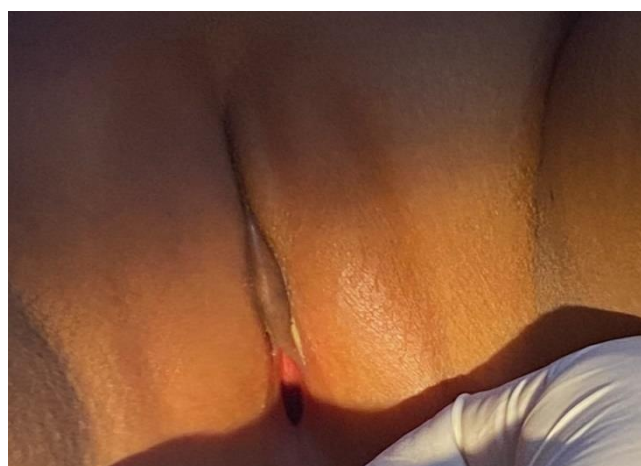


Figure 2. Clinical appearance of the external genitalia in a patient with 46,XY gonadal dysgenesis, showing a hypertrophic clitoris, short perineum, and infantile vaginal introitus, findings consistent with ambiguous genitalia.

DISCUSSION

46,XY disorders of sex development (DSD) represent a heterogeneous group of conditions requiring a complex clinical, surgical, endocrinological, and psychosocial approach. Multiple clinical and genetic variants have been reported in the literature, underscoring the diagnostic challenge and the need for multidisciplinary evaluation.^{2,3} Brambilla et al. (2022) described a 17-year-old patient with 46,XY DSD due to 17 β -HSD3 enzyme deficiency, whose management included clitoroplasty, hormone replacement therapy, and psychological support. The authors emphasized the importance of avoiding early irreversible surgeries except when vital risk exists.⁵ This case highlights the need for individualized care and avoidance of irreversible procedures unless necessary for health reasons. In contrast, our patient underwent bilateral orchiectomy and penectomy at 2 years of age solely for sex assignment purposes, without prior gonadal biopsy—reflecting practices now considered outdated and not recommended.

Hou et al. (2021) evaluated 112 patients with 46,XY DSD and found that gender reassignment was consistent with gender roles in childhood, with no cases of gender dysphoria documented in patients older than 8 years. The authors emphasized that molecular diagnosis and gonadal function are key factors in clinical decision-making and stressed the importance of long-term follow-up.⁶ Our patient initially lacked access to molecular testing due to economic limitations; however, a genetic panel covering 53 DSD-associated genes was later found in her medical record, showing negative results with no identifiable pathogenic variants. This finding reinforces that even with first-line molecular studies, the etiology may remain undefined, consistent with reports in the literature showing that the confirmed diagnostic yield in 46,XY DSD remains below 50%. Furthermore, she presented with significant psychosocial impact, including depression and anxiety—findings rarely described but highly relevant in clinical practice.

In a more recent cohort, Ding et al. (2025) analyzed 21 patients with 46,XY DSD without a uterus and identified genetic variants in genes involved in androgen synthesis and gonadal development, including novel mutations. This underscores the utility of reverse phenotyping and advanced sequencing techniques.³ In our case, the diagnosis was based on a 46,XY karyotype with a positive SRY gene and clinical findings consistent with gonadal dysgenesis, without additional molecular confirmation, which limits etiological characterization but did not preclude comprehensive management.

From an integrated management perspective, Wisniewski et al. (2019) emphasized that managing 46,XY DSD requires an interdisciplinary team and that complete hormonal and, whenever possible, molecular studies should be conducted prior to sex assignment. They also highlighted the importance

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of mental health support and the need to assess long-term quality of life and fertility.⁷ In accordance with these recommendations, our patient is currently receiving hormone replacement therapy, calcium and vitamin D supplementation for bone density reduction (−17%), and multidisciplinary follow-up with Gynecology, Endocrinology, Psychiatry, and Plastic Surgery—illustrating a contemporary multidisciplinary approach despite early surgical intervention inconsistent with current guidelines.

Finally, Yu and Liu (2024) reported two cases of 46,XY DSD managed with prophylactic gonadectomy and long-term estrogen therapy, confirming the tumor risk associated with dysgenetic gonads.⁸ In our patient, early childhood gonadectomy prevented tumor complications but necessitated continuous estrogen therapy to induce secondary sexual characteristics, maintain bone health, and improve quality of life.

The combination of clinical, endocrinological, and imaging findings supports the diagnosis of 46,XY gonadal dysgenesis, despite a negative molecular panel. The etiology likely involves variants not detected by the genes analyzed, reflecting the genetic heterogeneity of these entities.

Overall, current evidence reinforces that management of patients with 46,XY DSD must be comprehensive, including molecular diagnosis whenever possible, endocrinological monitoring, psychological support, and family counseling. Our case illustrates the particular challenges of late diagnosis, limited diagnostic resources, and significant psychosocial impact—highlighting the need for individualized, multidisciplinary approaches that integrate medical and psychosocial perspectives.

This case contributes to the literature by documenting a comprehensive multidisciplinary follow-up involving endocrinology, gynecology, psychiatry, and plastic surgery, along with bone supplementation and psychosocial support. As limitations, we note the absence of gonadal histopathology, delayed initiation of hormone replacement therapy, and lack of broader molecular testing (exome or whole-genome sequencing), which restricts etiologic characterization.

CONCLUSION

This case of 46,XY gonadal dysgenesis illustrates the diagnostic, therapeutic, and ethical challenges associated with disorders of sex development. Despite having a 46,XY karyotype and a negative genetic panel, the diagnosis was established clinically, reflecting the current limitations of molecular genetics. A comprehensive and multidisciplinary management plan—including hormone replacement therapy, bone supplementation, psychological support, and continuous follow-up—improved the patient's quality of life and emotional well-being.

This report emphasizes the need for timely diagnosis, ethical and reflective decision-making regarding irreversible

interventions, and integral care encompassing medical, psychological, and social perspectives.

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Conflict of Interest: None.

Ethical Considerations: The patient was fully informed about her diagnosis, interventions, and potential risks. Written informed consent was obtained for all surgical and anesthetic procedures, as well as for the publication of this case report, in accordance with the ethical principles of the Declaration of Helsinki and the institutional regulations of the hospital.

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