DOI: https://dx.doi.org/10.47746/FMCR.2025.6609

Natural History of 46, XX Testicular Disorder of Sex Development: Case Report from Birth to Puberty

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Received: 11 December 2025; **Accepted:** 31 December 2025

ABSTRACT

46,XX testicular disorder of sex development (DSD) is a rare condition where individuals with a 46,XX karyotype develop testicular differentiation and virilization. This anomaly is mainly caused by the translocation of the SRY gene onto the X chromosome, leading to testicular differentiation. Diagnosis typically occurs in adulthood, often during infertility evaluations. This case report describes a prenatal diagnosis of an SRY+XX fetus and follows his clinical evolution to puberty. Hormonal analysis were normal at birth, but during puberty showed testicular failure and hypergonadotropic hypogonadism. Nonetheless, hormone replacement therapy was not required, as his testosterone levels were adequate and his growth progression remained within the expected range. This case highlights the importance of prenatal diagnosis and long-term endocrinological follow-up in managing progressive testicular dysfunction and fertility implications associated with SRY+XX.

Keywords: *46,XX, Testicular DSD, SRY Translocation, Prenatal Diagnosis, Hypergonadotropic Hypogonadism, SRY+XX*

Introduction

46,XX testicular disorder of sex development (DSD) is a rare condition in which individuals with a 46,XX karyotype undergo testicular differentiation and virilization. This condition, also known as SRY+XX, XX male syndrome or "De la Chapelle syndrome," has an estimated incidence of 1 in every 20,000 male newborns. In approximately 80% of cases, this condition results from the translocation of the SRY gene

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from the Y chromosome to the X chromosome during paternal meiosis, leading to testicular differentiation despite the absence of a complete Y chromosome (Délot and Vilain, 1993-2025).

Human sex differentiation from bipotential gonads to testes or ovaries is a complex, sequential, and hierarchical process, involving the interaction of several genes. The expression of the sex-determining region Y gene (SRY) initiates a cascade of testicular formation pathways via the upregulation of SRY-box-9 (SOX9) and other SOX family members, including SRY-box-3 (SOX3), SRY-box-8 (SOX8), and SRY-box-10 (SOX10) (Ferrari *et al*., 2024).

Testicular differentiation can also occur in SRY-negative individuals due to increased expression of SOX3, SOX9, and specific heterozygous pathogenic variants in NR5A1 or WT1. These cases often present with genital ambiguity, hypospadias, cryptorchidism, short stature and gynecomastia (Sreenivasan *et al*., 2022).

In SRY+XX patients, during prenatal life and early childhood, Sertoli and Leydig cells are functional, with normal production of anti-müllerian hormone (AMH), testosterone and dihydrotestosterone. Therefore individuals typically present with normal male internal and external genitalia, descended testes, and absence of müllerian structures. At early stages of puberty, normal penis development and length are expected, as well as standard virilization. Later on, similar to individuals with Klinefelter syndrome, the presence of an additional X chromosome leads to progressive hyalinization of the seminiferous tubules resulting in persistently small testicles and spermatogenic failure due to significant germ cell loss during meiosis (Akar *et al*., 2020).

Vorona, *et al*. (2007) compared 11 SRY+XX males to age-matched controls and patients with Klinefelter syndrome, and stated that SRY+XX males tend to be significantly shorter than controls and Klinefelter patients. They suggested that this could partly be explained by the absence of Y chromosome material, and that therefore genes within the Y chromosome could play a role in the control of growth in male individuals.

The natural history of these patients is developing into hypergonadotropic hypogonadism, some of them showing an impaired testosterone production, resulting, when untreated, in gynecomastia, lack of pubertal spurt, and sparse pubic hair (Délot and Vilain, 1993-2025).

Genes related to spermatogenesis are located on the long arm of the Y chromosome, at the AZFa, AZFb, and AZFc loci. These genes are absent in SRY+XX individuals, leading to irreversible azoospermia and infertility (Shen *et al*., 2023).

Prenatal diagnosis of SRY+XX is rare, posing significant challenges for both genetic counseling and clinical management. Despite advances in understanding the genetic and hormonal mechanisms underlying SRY+XX patients, most published reports describe patients identified during adulthood, often after the development of hypergonadotropic hypogonadism or infertility. Consequently, there is limited information on the early clinical course, timing of pubertal development, and potential opportunities for anticipatory management in these patients. This report provides a rare opportunity to follow an SRY+XX individual from prenatal diagnosis through puberty.

Case Presentation

A 35-year-old pregnant woman underwent an amniocentesis at 23+2 weeks of gestation due to an increased risk for chromosomal abnormalities.

Cytogenetic analysis on amniotic fluid revealed an apparently normal 46,XX karyotype, although ultrasound examination performed at 20 weeks of gestation identified male external genitalia, including a well-formed penis and scrotum, with no structural anomalies detected. The discrepancy between the karyotype and ultrasound findings was later confirmed by a second amniocentesis, prompting molecular genetic testing to rule out congenital adrenal hyperplasia (CAH) caused by a CYP21 mutation. Results were normal for both the patient and the parents. No aromatase inhibitor treatments or any other androgenic drugs had been previously administered to the mother, she had no history of consanguinity or other health issues and had a normal previous pregnancy.

The infant was delivered at 38+4 weeks of gestation via eutocic labor. He presented a normal birth weight of 2,820 g (-1.04 SD) and a normal length of 49 cm (-0.46 SD). Physical examination at birth revealed normal male external genitalia, normal penile length of 3 cm, and palpable testes of 1.5 cc within the scrotum. No physical abnormalities were noted (Fig. 1). An abdominal ultrasound was performed, showing normal adrenal glands and no abnormalities. Testicular function was evaluated through hormonal testing conducted between 24 and 36 hours after birth, with the following adequate results: Testosterone: 351 ng/L, Luteinizing hormone (LH): <0.1 U/L, Follicle-stimulating hormone (FSH): <0.1 U/L. Androstenedione and 17-Hydroxyprogesterone were also normal: 2.7 ng/mL and 2.67 ng/mL respectively.

Postnatal genetic studies were performed on peripheral blood. G-banded karyotype analysis with a 400-550 band resolution confirmed the apparently 46,XX normal result. Fluorescence in situ hybridization (FISH) analysis with probes for the SRY gene and the X-chromosome centromeric region detected the presence of the SRY gene at the terminal region of the short arm of one X chromosome, confirming an SRY+ 46,XX karyotype. The FISH study on peripheral blood was also carried out on the patient's father, showing the presence of the SRY gene at the expected location of the Y chromosome. Therefore, the derivative SRY+X chromosome observed in the child resulted from a translocation between the short arms of chromosomes X and Y during paternal gametogenesis.

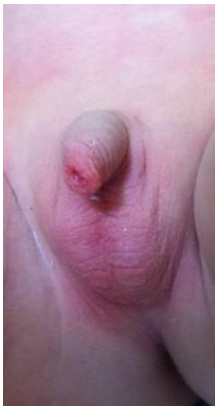

Figure 1: Appearance of the patient's external genitalia at 4 months of age, presented a normal penis length of 3cm and descended testicles of 1.5cc.

The parents received genetic counseling regarding the diagnosis of SRY+XX, discussing its potential implications, prognosis, and management strategies.

Throughout infancy and early childhood, the child's growth and hormonal levels were within normal limits. During the early stages of puberty (12-13 years of age), the patient exhibited a normal penile length (Tanner stage G2), and appropriate testicular volume of 6/8cc. Hormonal analyses were concordant (Table 1). The peak growth spurt was 7.8 cm/year (0.63 SD) at age 13. The genetically predicted height was: -2 SD).

However, at 13 years and 6 months, the patient exhibited stagnation of testicular volume, maintaining 6/8 cc. Hormonal analysis revealed a marked decline in inhibin B levels and a hypergonadotropic hypogonadism with preserved Leydig cell function (Table 1). Physical examination showed no gynecomastia and a Tanner stage V, with normal pubic hair and penis length (Fig. 2). Given these findings, close monitoring was initiated, with hormonal analyses and anthropometric measurements

every 4 to 6 months to promptly detect declining testosterone levels or growth velocity, which could indicate the need for hormone replacement therapy.

Table 1: Longitudinal hormonal profile showing normal neonatal testosterone levels during mini-puberty, followed by progressive hypergonadotropic hypogonadism, characterized by a marked decline in inhibin B levels and a significant increase in FSH, while Leydig cell function remains preserved, as reflected by testosterone concentrations within the normal range.

	Age								
	24h	2y	12y	13y	13y 6m	14y 6m	15y	15y 8m	Normal values for adult males
Luteinizing hormone (U/L)	<0.1		0.77	2.55	9.22	8.7	8.98	11	1.3-8
Follicle-stimulating hormone (U/L)	<0.1		1.24	4.29	29.89	30.58	28.24	27.77	1.6-11
Testosterone (ng/mL)	351		22.9		350	96	230.5	309.1	230-710
Inhibin B (pg/mL)		143	253	193		16	19	15.6	Mean 166 (range: 25-325)

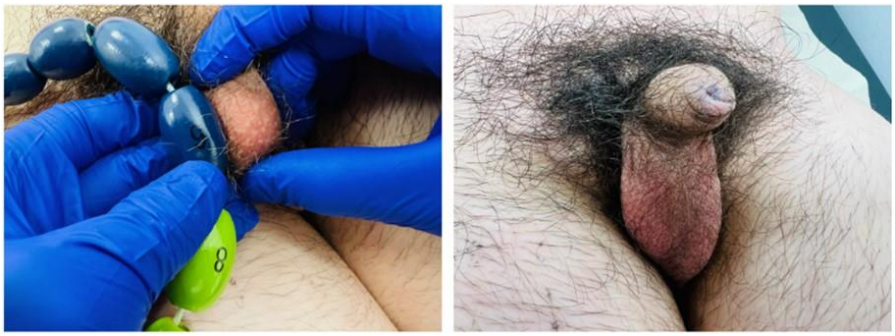

Figure 2: Appearance of the patient's external genitalia at 13 years and 6 months of age, Tanner stage V, normal pubic hair and penis length, but stagnation of testicular volume at 6cc.

Currently, the patient is 15 years and 6 months old, and his hormonal levels have remained stable (Table 1). He reports regular erections, has a testicular volume of 10cc, and a normal penile length. Anthropometric measurements have confirmed an appropriate pubertal growth spurt (Fig. 3). Follow-up will continue biannually until final adult height is reached, followed by annual evaluations into adulthood.

To refine the diagnosis, we recently reanalyzed the patient's peripheral blood sample using modern cytogenetic and molecular cytogenetic approaches, which confirmed an SRY+ 46,XX testicular disorder of sex development (DSD). G-banded karyotype analysis at a 550-band resolution revealed an apparently normal 46,XX karyotype (Fig. 4), aligned with the results obtained from the prenatal karyotype. FISH analysis with probes for the SRY gene and the X-chromosome centromeric region detected the presence of the SRY gene at the terminal region of the short arm of one X chromosome, confirming the 46,XX.ish der(X)t(X;Y)(p22.?3;p11.?2)(SRY+,DXZ1+) karyotype (Fig. 5). Comparative genomic hybridization (CGH)

microarray analysis demonstrated a loss of approximately 3.6 Mb in the terminal Xp22.33 region and a gain of about 9.3 Mb in the Yq11.21–q11.23 region, including the SRY gene (Fig. 6-7).

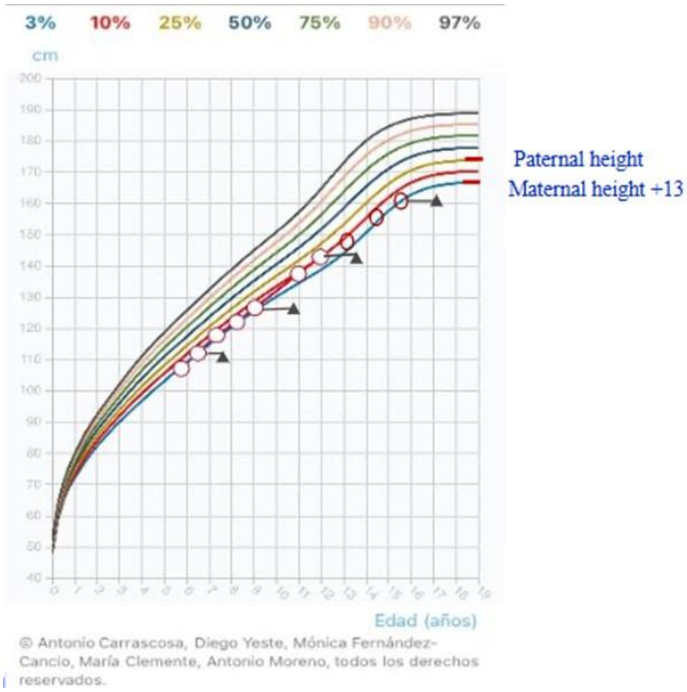

Figure 3: Growth chart showing a correct prepubertal growth pattern as well as a normal pubertal spurt, given preserved Leydig cell function. Final predicted height within the expected range for genetic height.

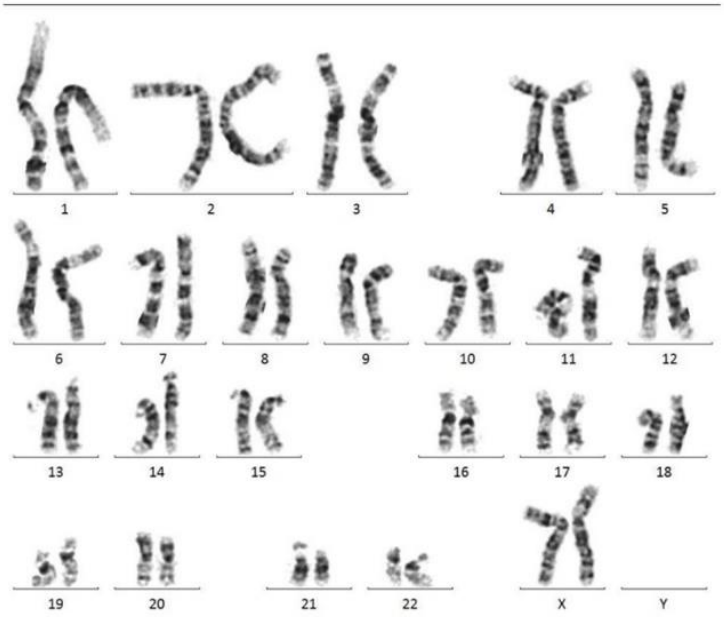

Figure 4: G-banded karyotype analysis at a 550-band resolution revealed an apparently normal 46XX karyotype, underscoring the need for complementary molecular cytogenetic techniques to establish the diagnosis.

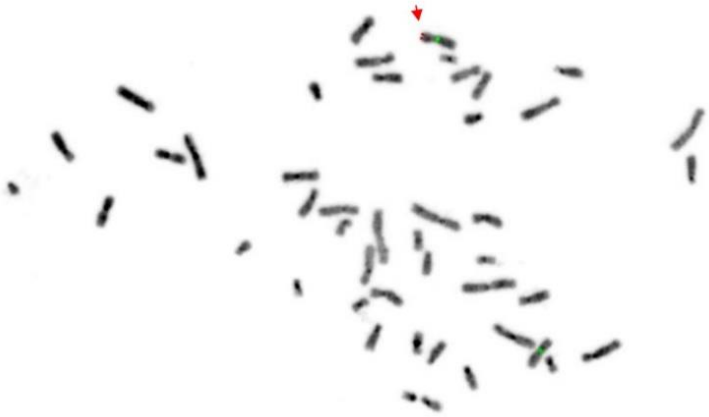

Figure 5: FISH analysis with probes for the SRY gene (red) and the X-chromosome centromeric region (green). Confirming the presence of the SRY gene at the terminal region of the short arm of one X chromosome (marked with a red arrow).

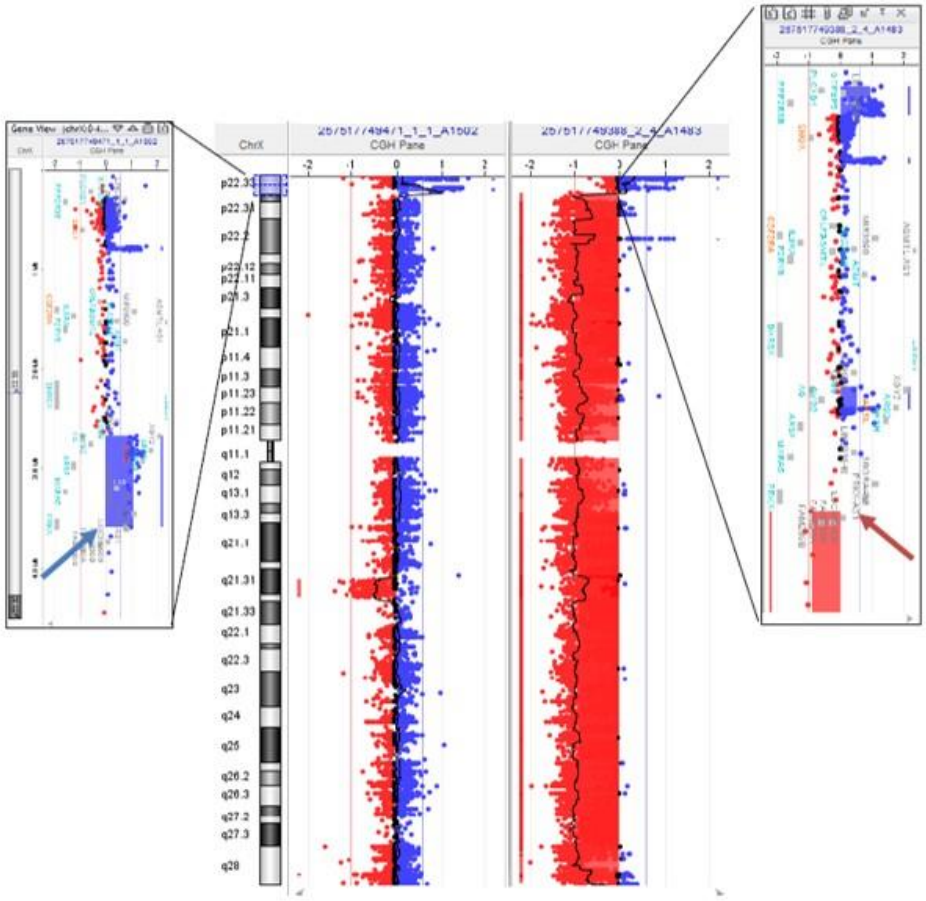

Figure 6: X chromosome profile of the patient (DNA marked with Cy3, red) hybridized against a reference with an XX chromosomal complement (A1502-1-1, left) and against a reference with an XY chromosomal complement (A1483-2-4, right). This comparative approach allows precise delineation of the deleted Xp segment and accurate localization of the proximal breakpoint, thereby defining the exact region of the X chromosome involved in the translocation (left image, blue arrow; right image, red arrow.

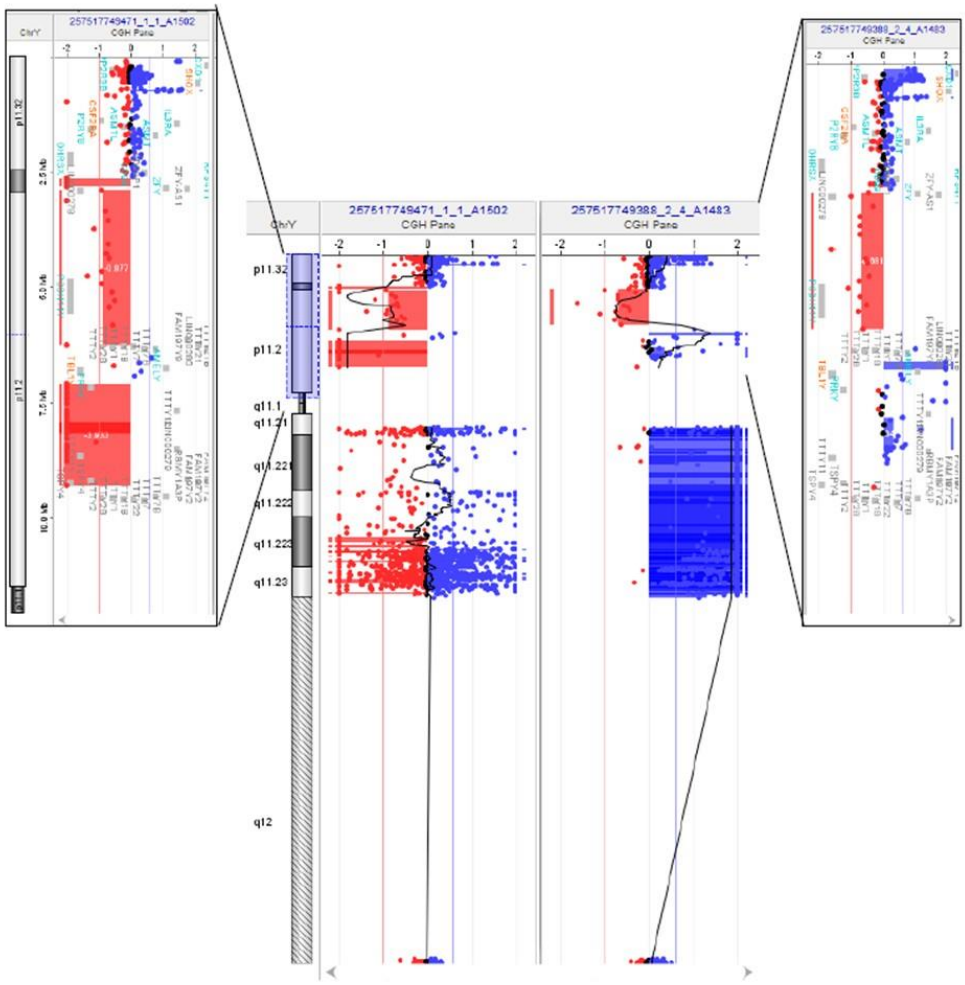

Figure 7: Y chromosome profile of the patient (DNA marked with Cy3, red) hybridized against a reference with an XX chromosomal complement (A1502-1-1, left) and against a reference with an XY chromosomal complement (A1483-2-4, right). This analysis enables precise identification of the Y-chromosomal region gained in the patient and determination of the specific Y-chromosome segment translocated onto the X chromosome.

Discussion

SRY+XX is a rare genetic condition and an important cause of hypergonadotropic hypogonadism and infertility. Diagnosis is frequently delayed or missed, as most cases are identified in adulthood during evaluations for infertility, given the absence of Y chromosome genes essential for spermatogenesis. As a result, the clinical spectrum of this condition has been defined by late-diagnosed cases, limiting insight into its early natural history.

Differential diagnosis of prenatal virilization in a 46,XX fetus should primarily consider congenital adrenal hyperplasia (CAH) and other androgen excess disorders during pregnancy. Once CAH is ruled out, the differential should include disorders of gonadal differentiation such as XX gonadal dysgenesis, 46,XX

testicular DSD, and 46,XX ovotesticular DSD, as well as syndromic conditions like mutations on NR2F2 and RSPO1 genes (Guerrero-Fernandez *et al*., 2018; Acién and Acién, 2020). Another potential cause of fetal virilization is maternal exposure to aromatase inhibitors. Moran *et al*. reported a case of a 46,XX infant with virilization secondary to maternal aromatase inhibitor therapy for breast cancer during pregnancy, high maternal testosterone levels led to significant fetal androgen exposure, which caused virilization in the fetus that diminished after birth (Moran *et al*., 2023). In the present case, the absence of maternal androgen exposure and exclusion of CAH, together with normal male external genitalia, strongly supported the diagnosis of 46,XX testicular DSD, later confirmed by targeted molecular testing.

In some SRY+XX patients with large chromosomal rearrangements, conventional karyotyping may be sufficient to suggest the diagnosis. However, in other cases, karyotype may appear completely normal, making additional molecular cytogenetic techniques essential to reach the diagnosis, close communication between the referring clinician and the molecular geneticist is needed to guide appropriate diagnostic testing.

Prenatal identification of SRY+XX is rare, often arising when discrepancies between chromosomal sex and ultrasound findings are detected, as occurred in the present case, but most pregnancies do not undergo invasive genetic testing unless considered high risk. Recently there has been an increased use of non-invasive prenatal testing (NIPT), NIPT analyzes cell-free fetal DNA (cffDNA) circulating in maternal blood to detect common fetal chromosomal aneuploidies, using massively parallel sequencing or targeted analysis to quantify and assess fetal DNA fragments. This test also predicts the genetic sex of the fetus by detecting the presence or absence of Y chromosome–specific DNA sequences in cffDNA circulating in maternal plasma. If Y chromosome–specific sequences (such as SRY) are detected, the fetus is predicted to be male; if these sequences are absent, the fetus is predicted to be female (Smet *et al*., 2020).

Despite these advances, the real-world feasibility of early diagnosis remains limited. Access to NIPT varies widely across healthcare systems and socioeconomic contexts, therefore limitations in healthcare access may contribute to underdiagnosis, as in most cases prenatal ultrasound identifies these fetuses as male and no other analyses are performed, delaying diagnosis until adulthood when clinical manifestations become apparent.

Early diagnosis nonetheless provides substantial clinical benefits. It allows timely parental counseling regarding prognosis, long-term expectations, and management strategies, enabling informed decision-making from infancy. SRY+XX is typically sporadic, resulting from a de novo translocation of the SRY gene onto the X chromosome, and the recurrence risk for parents is considered low.

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To our knowledge, cases diagnosed as early as the prenatal or neonatal period are scarcely reported in the literature, which precludes direct comparison with similarly early-diagnosed individuals. Only a limited number of case series have described the clinical spectrum of SRY+XX, and all of them focus almost exclusively on adults diagnosed during infertility evaluations, thereby reflecting the consequences of delayed diagnosis rather than the natural history of the condition from early life.

A retrospective study analyzing 10 SRY+XX cases found that affected individuals typically presented with small testes (≤5 mL), azoospermia, and hypergonadotropic hypogonadism, with some exhibiting reduced secondary sexual characteristics, decreased body hair, and gynecomastia (Akinsal *et al*., 2017). Similarly, a Turkish study of nine patients reported consistent findings (Akar *et al*., 2020). An Iranian study analyzing 8,114 males with azoospermia identified 57 cases of 46,XX karyotype, 90% of whom were SRY+, with normal male phenotype but had atrophic testes and hormonal profiles indicative of hypergonadotropic hypogonadism (Mohammadpour *et al*., 2017). Lastly a systematic review analyzing 37 studies described 64 adult patients with 46,XX testicular DSD. Hair distribution was normal in 74.3% of patients, gynecomastia was present in 43.6%, and no patients had normal testicular volume. The hormonal profile of the patients revealed the common presence of hypergonadotropic hypogonadism and the SRY gene was detected in 89.5% of cases (Terribile *et al*., 2019). Across these studies, testicular biopsies, when performed, revealed seminiferous tubule hyalinization and complete germ cell loss.

In contrast to these adult series, the present case illustrates the potential clinical impact of prenatal diagnosis and close longitudinal follow-up from birth. In our case, the patient exhibited normal growth and development both during infancy and puberty due to preservation of Leydig cell function during these periods. However, testosterone replacement therapy might be essential to some patients with hypergonadotropic hypogonadism with impaired Leydig cell function, to induce puberty, maintain secondary sexual characteristics, support bone health, and improve quality of life (Nordenström *et al*., 2022).

Regular monitoring of hormone levels, bone density, and assessment of libido, energy, and presence or progression of gynecomastia are essential components of long-term care, as well as fertility counseling given the inherent infertility associated with this condition. In patients requiring hormonal replacement therapy, testosterone levels should be monitored every 3 months (prior to the following injection) until testosterone dose is optimized; then spaced to every 6 to 12 months (Nordenström *et al*., 2022). In cases where gynecomastia persists despite testosterone therapy, reduction mammoplasty may be considered. Standard treatment for osteopenia, hypospadias, and cryptorchidism should be carried if present. Only one case of a germ cell tumor has been reported in a SRY+XX patient presenting with ambiguous genitalia

(Carcavilla *et al*., 2008). As these appear to be rare events, no consensus tumor screening protocol has been recommended to date for these individuals.

Regarding side effects of testosterone therapy, the most frequently reported include acne and erythrocytosis, the latter of which may occur at any time during treatment; current recommendations advise temporary discontinuation of therapy if hematocrit exceeds 54%. In addition, assessment of lipid profile is recommended, as testosterone therapy may be associated with a reduction in high-density lipoprotein (HDL) cholesterol, whereas its effects on low-density lipoprotein (LDL) cholesterol and triglyceride levels are generally minimal when administered at replacement doses. Liver function tests should also be periodically evaluated, particularly to ensure treatment safety, although clinically significant hepatotoxicity is uncommon with standard replacement regimens.

Conclusion

SRY+XX is a rare genetic condition that causes hypergonadotropic hypogonadism and infertility. Advances in NIPT and early ultrasound evaluations may lead to increased prenatal identification of SRY+XX cases. Early diagnosis facilitates genetic counseling, endocrinological monitoring, and timely therapeutic interventions, ultimately optimizing patient care and quality of life.

Informed Consent: Written informed consent was collected from the patient.

Conflict of Interest: None declared

Financial Disclosure: The authors declared that this study received no financial support.

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