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Antenatal Diagnosis of Disorders of Sex Development Associated with Trisomy 13: A Case Report

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Abstract **Case Report**

Introduction**:* Disorders of sex development (DSD) are rare congenital conditions characterized by atypical genital, gonadal, or chromosomal sex, with an incidence of 1/10,000 births. Antenatal ultrasound can detect ambiguous genitalia, prompting specialized evaluation. ***Case Presentation: A 30-year-old primigravida's fetus was diagnosed with ambiguous genitalia (micropenis, hypospadias) at 22 weeks' gestation via ultrasound. Trophoblast biopsy confirmed trisomy 13, and postnatal examination revealed additional dysmorphic features. ***Results:*** Multidisciplinary antenatal management included specialized ultrasound and genetic counseling, with postnatal confirmation of DSD and trisomy 13. ***Conclusion:*** This case highlights the importance of antenatal ultrasound in detecting DSD, the association with trisomy 13, and the need for comprehensive genetic and multidisciplinary evaluation.

Keywords: Disorders of sex development, ambiguous genitalia, trisomy 13, ante- natal ultrasound, congenital adrenal hyperplasia, genetic counseling.

1. INTRODUCTION

Disorders of sex development (DSD) encompass a group of rare congenital conditions defined by atypical development of chromosomal, gonadal, or anatomical sex, with an estimated incidence of 1/10,000 live births [1]. Clinically, DSD present as ambiguous external genitalia or discordance between chromosomal, gonadal, and phenotypic sex [2]. These anomalies arise from disruptions in the complex process of sexual differentiation, which occurs in four key stages: [1] establishment of chromosomal sex at fertilization (46,XX or 46,XY), [2] development of the bipotential gonad, [3] differentiation of the gonad into testes or ovaries, and [4] hormone-dependent differentiation of internal and external genitalia [3].

The first stage, chromosomal sex determination, depends on the contribution of an X or Y chromosome from the spermatozoon, resulting in a 46,XX (female) or 46,XY (male) karyotype. The second and third stages involve gonadal development, driven by genes such as SRY (on the Y chromosome) for testicular differentiation or WNT4 and RSPO1 for ovarian differentiation [4]. The final stage relies on hormonal signaling: anti-Mu¨llerian hormone (AMH) and testosterone from testicular cells cause regression of Mu¨llerian ducts and masculinization of Wolffian ducts, respectively, while dihydrotestosterone (DHT) shapes external genitalia [3]. In the absence of androgens, female genitalia develop spontaneously.

DSD are classified into 46, XX DSD (e.g., congenital adrenal hyperplasia), 46, XY DSD (e.g., androgen insensitivity syndrome), ovotesticular DSD, and chromosomal DSD (e.g., Klinefelter syndrome) [2]. Antenatal ultrasound can detect ambiguous genitalia, such as micropenis, hypospadias, or clitoromegaly, prompting specialized evaluation [5]. DSD are frequently associated with syndromes like trisomy 13, which presents urinary tract and genital anomalies in 30–50% of cases [6]. This case report describes the antenatal diagnosis of DSD in a fetus with trisomy 13, emphasizing ultrasound findings, genetic confirmation, and multidisciplinary management.

2. CASE PRESENTATION

A 30-year-old primigravida with no significant medical history presented for a routine second-trimester ultrasound at 22 weeks' gestation. The ultrasound revealed ambiguous external genitalia, characterized by

a micropenis (short penile length ¡5 mm), hypospadias, and a bifid scrotum. The uterus was not visualized, and testicular descent was absent. Amniotic fluid volume was nor- mal (amniotic fluid index: 11 cm). Additional findings suggestive of trisomy 13 included a frontonasal malformation and unilateral renal ectopia.

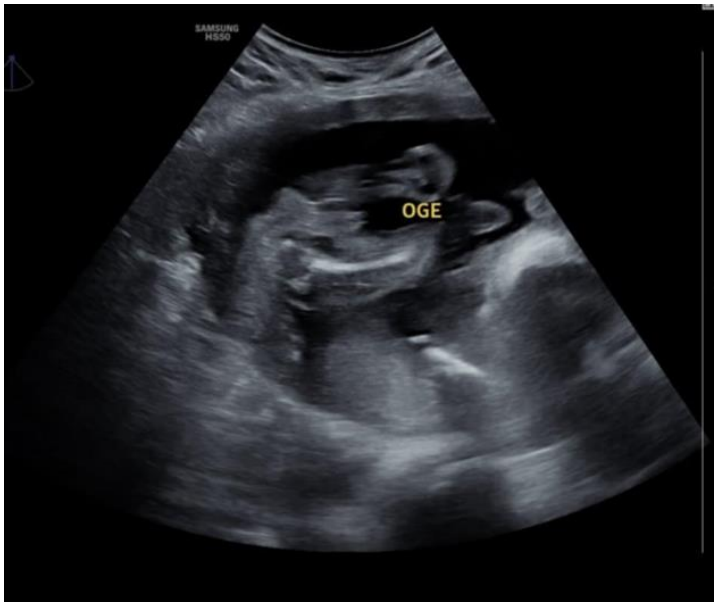

Figure 1: Sagittal ultrasound at 22 weeks showing micropenis and hypospadias

A specialized morphological ultrasound at 24 weeks confirmed the genital anomalies and identified additional dysmorphic features, including a bomb-shaped forehead and flattened nasal bridge. Trophoblast biopsy was performed, revealing a 46,XY karyotype with trisomy 13. Serial ultrasounds at 26, 28, and 32 weeks showed persistent genital anomalies (micropenis, absent testicular descent) and stable renal ectopia with mild left hydronephrosis. No uterus or ovaries were visualized, suggesting a male phenotypic presentation with internal anomalies. The patient received multidisciplinary counseling from maternal-fetal medicine, pediatric

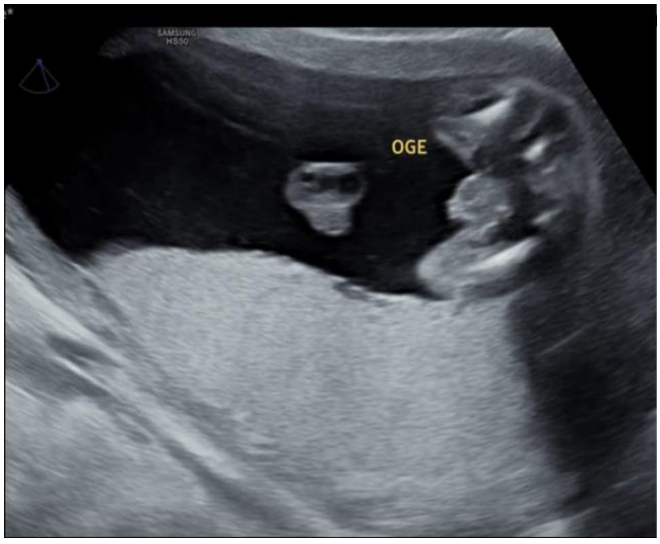

Figure 2: Transverse ultrasound at 22 weeks confirming bifid scrotum

endocrinology, urology, and genetics teams. Genetic counseling highlighted the poor prognosis of trisomy 13, including neurodevelopmental impairment and a high risk of perinatal mortality. Delivery occurred at 36 weeks via cesarean section due to fetal distress, resulting in a male neonate (birth weight: 2.8 kg). Postnatal examination con- firmed ambiguous genitalia (micropenis, hypospadias, empty scrotum) and dysmorphic features (bomb-shaped forehead, low-set ears). Abdominal ultrasound revealed right renal ectopia and left hydronephrosis, with no uterus or ovaries. The neonate developed respiratory distress and hy- poglycemia, requiring neonatal intensive care. Sadly, the

infant passed away at 10 days of age due to multisystem failure associated with trisomy 13.

3. DISCUSSION

Disorders of sex development (DSD) result from disruptions in the four-stage process of sexual differentiation, leading to ambiguous genitalia or discordance between chromosomal, gonadal, and phenotypic sex [1]. The case presented here illustrates a 46,XY DSD with ambiguous genitalia (micropenis, hypospadias, bifid scrotum) associated with trisomy 13, a chromosomal anomaly linked to genital and systemic malformations [6].

Antenatal ultrasound is critical for detecting DSD, with findings such as micropenis, clitoromegaly, or absent testicular descent prompting further evaluation [5]. In this case, sagittal and transverse ultrasound views confirmed genital anomalies, while additional findings (renal ectopia, dysmorphic features) suggested a syndromic etiology.

DSD are classified based on karyotype and gonadal histology. 46,XX DSD, such as congenital adrenal hyperplasia (CAH), result from virilization of external genitalia due to excess androgens, often caused by 21-hydroxylase deficiency (CYP21A2 mutation) [7]. 46,XY DSD, as seen in this case, involve under virilization due to defective androgen synthesis or action, or gonadal dysgenesis [2]. Ovotesticular DSD feature both ovarian and testicular tissue, while chromosomal DSD, such as Klinefelter syndrome (47,XXY), present hypogonadism and genital anomalies [8]. Trisomy 13, present in this case, is associated with ambiguous genitalia and hypospadias, particularly in deletions involving 13q34 [6]. The trophoblast biopsy confirming trisomy 13 was pivotal in guiding prognosis and management.

Antenatal management of DSD involves specialized ultrasound, amniocentesis, or chorionic villus sampling to assess karyotype and exclude aneuploidies [5]. In this case, the absence of a uterus and testicular descent suggested a male phenotype with internal anomalies, consistent with 46,XY DSD. The association with trisomy 13 necessitated comprehensive genetic counseling, as the condition carries a high risk of neurodevelopmental impairment and early mortality [6]. A 2019 case report from the Pan African Medical Journal described a similar presentation: a neonate with 46,XY, r(13) karyotype, ambiguous genitalia (hypoplastic penis, hypospadias), and dysmorphic features, highlighting the role of autosomal anomalies in DSD [9].

Postnatal management of DSD requires a multidisciplinary approach, including endocrinology, urology, and psychology, to address genital anomalies, hormonal imbalances, and psychosocial needs [3]. In CAH, glucocorticoid and mineralocorticoid replacement is critical to prevent adrenal crises [7]. In 46,XY DSD, surgical correction of hypospadias or

cryptorchidism may be considered, though timing remains controversial [10]. In this case, the neonate's early demise due to trisomy 13 precluded long-term management, underscoring the severe prognosis of the condition.

This case highlights several key points. First, antenatal ultrasound is essential for detecting DSD and associated anomalies, guiding diagnostic workup. Second, trisomy 13 should be considered in cases of ambiguous genitalia with dysmorphic features, as autosomal anomalies can contribute to DSD [9]. Third, multidisciplinary management is critical to address the medical, ethical, and psychosocial complexities of DSD. Future research should focus on improving prenatal diagnostic techniques and standardizing management protocols for DSD in the context of chromosomal syndromes.

4. CONCLUSION

This case report describes the antenatal diagnosis of 46,XY DSD with ambiguous genitalia in a fetus with trisomy 13, confirmed by trophoblast biopsy. Ultrasound findings of micropenis, hypospadias, and absent testicular descent, coupled with dysmorphic features and renal anomalies, prompted a comprehensive evaluation. The case underscores the role of antenatal ultrasound in detecting DSD, the association with trisomy 13, and the importance of multidisciplinary management. Clinicians should maintain a high index of suspicion for chromosomal anomalies in DSD and provide tailored genetic counseling to inform prognosis and decision-making.

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