DJOG Danish Journal of Obstetrics and Gynaecology

Prenatal diagnosis of monosomy X mosaicism – a clinical case report

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Abstract

Monosomy X mosaicism is known for its clinical variability. The condition depends on the proportion and distribution of 45,X cells in fetal tissues and is associated with significant risks of congenital heart defects, short stature, infertility, renal malformations, developmental delays and cognitive challenges.

We report a case of prenatal detection of monosomy X mosaicism in a male fetus identified following an abnormal non-invasive prenatal test (NIPT). A 21-year-old woman had a NIPT at 10 weeks of gestation on maternal request. A high risk of monosomy X (Turner syndrome) was reported. An invasive test was offered to confirm the finding, and a chorionic villus sampling (CVS) was performed at 13 weeks of gestation. Chromosomal micro-array of the CVS revealed a decreased Y chromosome ratio, corresponding to 43% of the placental cells. At 16 weeks of gestation, an early anomaly scan showed a normally developed fetus without structural abnormalities. Amniocentesis was performed and chromosomal micro-array revealed a true fetal monosomy X mosaicism consistent with a loss of the Y chromosome in 65% of the cells. A late fetal anomaly scan was performed in week 20, confirming normal appearance of male genitalia and no signs of structural abnormalities. The pregnancy was later complicated by fetal growth restriction and in gestational age 36+3 a caesarean section was performed due to flow alterations in the umbilical cord and pathological CTG (cardio-tocography). At birth, the child had normal genitalia, and no visible abnormalities. This case demonstrates the complexity in counselling parents following prenatal detection of monosomy X mosaicism, since the prognosis is uncertain due to mosaicism even when a high percentage of fetal mosaicism is present.

Keywords: Fetal mosaicism, Turner syndrome, Monosomy X.

Received: 19th of December 2025
Accepted: 30th of June 2026
Date of publication: 30th of June 2026
DOI: https://doi.org/10.56182/61etc843

INTRODUCTION

Turner syndrome (TS) is one of the most common sex chromosome aneuploidies, typically caused by complete or partial loss of one sex chromosome. TS is typically associated with a characteristic appearance of short stature, a broad chest and specific facial features, however, the risk of clinical manifestations such as infertility, cardiac and renal malformations, lymphedema, hearing loss, as well as behavioural, developmental and cognitive challenges is increased[1,2].

Monosomy X mosaicism is seen in some individuals with TS where two cell lines are present: One cell line with one X-chromosome (45,X) and one cell-line with normal sex chromosomes (46,XX or 46,XY). The mosaicism occurs early in fetal life due to an error in the cell division. Individuals with monosomy X mosaicism often has a milder phenotype than classic TS[1,3]. Patients with 45,X/46,XY mosaicism can present with a highly variable phenotype including genital ambiguity, male gender, and female gender with TS[4,5]. Additionally, there is no direct relationship between the degree of mosaicism and the presence of abnormalities found in the fetus or child which further complicates the counselling of expecting parents[5]. Hence, prenatal detection of fetal monosomy X mosaicism raises important questions regarding prognosis and outcome for the expecting parents. In the present case, we present a prenatal detection of fetal Turner mosaicism where the dominant cell line (45,X) is not the clinical phenotype, but an anatomically normal appearing male fetus. This illustrates the complexity in counselling expecting parents of a fetus with fetal monosomy X mosaicism.

CASE

A 21-year-old woman was referred for genetic counselling following an abnormal non-invasive prenatal test (NIPT) on maternal request at gestational week 10, which indicated monosomy X. A combined first trimester screening for aneuploidies at 12 weeks of gestation was normal with low risk of trisomy 13,18 and 21. The nuchal translucency thickness was normal (1.5 mm). Chorionic villus sampling was performed at week 13 and revealed a decreased Y chromosome ratio consistent with monosomy X in 43% of the cells, raising the possibility of confined placental mosaicism. To clarify if the mosaicism was present in the fetus, amniocentesis was performed at week 16. Micro-array of the fetal cells revealed fetal monosomy X mosaicism consistent with the presence of two cell lines present 65% 45,X and 35% 46,XY.

An anomaly scan at week 16 showed normal male genitalia, and no signs of Turner stigmata on ultrasound. Genetic counselling was provided, and possible scenarios of fetal affection was discussed with the parents, including risk of ambiguous gender, male fetus with possible infertility or female gender with TS.

A second-trimester scan at week 20 confirmed normal fetal growth and anatomy of a male fetus. Fetal growth restriction was identified at gestational week 29 and the fetus remained growth restricted (ranging between -27% to -17%) until birth. The fetus was delivered by caesarean section in gestational week 36+3 due to flow class 1-2 in the umbilical artery, reduced fetal movements and pathological CTG.

The boy was born with a birth weight of 2445 grams. The postnatal examination was normal, and male genitalia appeared normal with both testes present in the scrotum.

DISCUSSION

Counselling of parents following prenatal diagnosis of 45,X/46,XY mosaicism is difficult. The prognosis is highly variable and the degree of mosaicism in amniotic fluid is a poor predictor of outcome[5]. In addition, current evidence on outcome is highly diverging whether they are based on prenatal or postnatal diagnosis[2,6,7].

In retrospective studies of outcome in prenatally diagnosed 45,X/46,XY fetuses, approximately 89-95 % of the fetuses have normal appearance of the male genitalia, and only 5-10 % have ambiguous or female genitalia[5,6,8]. However, the studies also report high rates of abortion (up to 83%), which is

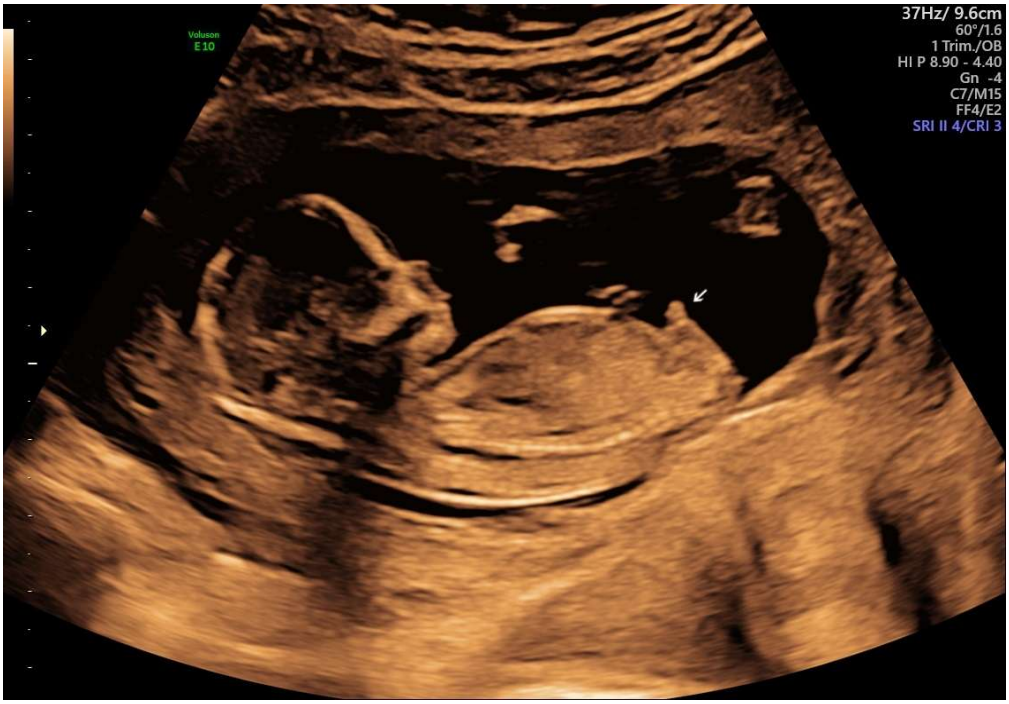

Figure 1: Ultrasound scan at 14+0 gestational weeks with visible male gender (marked with an arrow)

either due to termination of pregnancy or to fetal loss possibly due to a more severe phenotype[5,8,9]. In contrary, large retrospective studies of monosomy X mosaicism 45,X/46,XY have demonstrated that up to 50% of cases are diagnosed postnatally[10]. Most of these cases are found due to either short stature in childhood or infertility in adulthood[7,11,12]. Hence, postnatal detection of monosomy X mosaicism may reflect cases with milder phenotypes[10]. In cases with 45,X/46,XY with normal external male genitalia, up to 27% have abnormal gonadal tissue with increased risk of carcinoma even before puberty[5,10]. In contrary, other studies report that the majority of cases with 45,X/46,XY have sufficient gonadal function to achieve spontaneous puberty, but may require fertility treatment later in life[7].

The marked variation in phenotypic appearance and the diversity in outcome in previous studies make prenatal assessment and counselling complex, since there is no consistent correlation between karyotype and phenotype. This case is noteworthy since the fetus, despite a high percentage of monosomy X cells, had no structural abnormalities and normal development of male genitalia.

CONCLUSIONS

This case contributes to the broader understanding of the diagnostic complexities and dilemmas in genetic counselling following a prenatal diagnosis of monosomy X mosaicism in 45,X/46,XY fetuses.

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