

Title: Fetal trisomy 9 in the setting of low risk NIPT aneuploidy screening.

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Background/Synopsis: Trisomy 9 is a rare chromosomal abnormality in which three copies of chromosome 9 are identified in some or all cells. It is characterized by organ system dysmorphism and CNS malformations, which in most cases lead to a miscarriage or mortality in early infancy. Complete trisomy 9 is associated with severe multisystem malformations, including craniofacial dysmorphism, cardiac anomalies, CDH, GU abnormalities and neuro-developmental delays. For cases of mosaic trisomy 9, fetal and neonatal survival rates are somewhat increased and the phenotype is highly variable depending upon the proportion of affected cells. These fetuses have IUGR, craniofacial abnormalities and congenital heart anomalies. If the neonate survives beyond early infancy, severe intellectual disabilities and health challenges are to be expected.

Objective/Purpose: To highlight the limitations of NIPT for evaluation of fetal chromosome abnormalities while also reviewing the concept of chromosome mosaicism and the significance of trisomy 9.

Case Presentation: The patient is a 19-year-old healthy, thin female, gravida 1 para 0 who presented at 12 weeks EGA for evaluation of fetal viability and early anatomy via ultrasound. The examination was normal. NIPT was negative, with a 5.4% fetal fraction, male sex predicted, low risk for 22q11.2 microdeletion. Positive carrier screen for cystic fibrosis gene mutation, low risk for fetal CF disease. MS-AFP was abnormal, MoM 2.77, risk for open neural tube defects of 1 in 175. At 19 weeks EGA, ultrasound revealed a fetus with IUGR and multiple fetal structural abnormalities including a Dandy-Walker malformation, echogenic kidneys and mesocardia with cardiomegaly. The patient opted for genetic amniocentesis. FISH results were negative for chromosomes 13, 18, 21, X and Y, sex male. PCR studies were negative for HSV 1/2, toxoplasmosis, CMV and parvovirus. Amniotic fluid AFP was elevated at 2.47 MoM, negative acetylcholinesterase.

Final chromosome analysis returned abnormal: 47, XY +9.

The patient's prenatal course was significant for worsening fetal IUGR and a greater constellation of fetal structural abnormalities including micrognathia, abnormal posturing of the hands and rocker bottom feet. By 28 weeks EGA, umbilical artery Dopplers revealed absent end and reverse diastolic flow, consistent with severe placental dysfunction. At 29 weeks EGA, an IUFD was noted. The patient was directed to the labor and delivery unit for induction of labor. The patient had an uncomplicated induction of labor with misoprostol cervical ripening and a cervical Foley balloon, and later oxytocin Rx

with an epidural. The patient had a spontaneous breech vaginal delivery of a male neonate, weight 797 g. Multiple neonatal dysmorphic features were noted at delivery. The placenta was notable for a 3rd percentile weight for gestational age, mild to moderate microcalcifications and a three-vessel umbilical cord. The patient was discharged home the following day in stable condition.

Conclusion: NIPT failure is a fairly common result that occurs in 1 - 5% of screening tests overall. False positive results are approximately 9 times more common than false negative results. False negative results may be due to a low fetal fraction, multiple gestations, maternal obesity, triploidy and confined placental mosaicism. Our patient had no significant risk factors for a false negative NIPT. A failed NIPT should lead to further genetic counseling and a rapid response to consider level 2 ultrasound and genetic amniocentesis if indicated by fetal anatomic findings and biometry. Ultrasound remains an indispensable screening modality for the detection of fetal aneuploidy.