

Fetal Trisomy 9 in the Setting of Low Risk NIPT Aneuploidy Screening

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Background

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

- To highlight the limitations of non-invasive prenatal testing (NIPT) for evaluation of fetal chromosome abnormalities.
- To review the concept of chromosome mosaicism and the significance of trisomy 9.

Case Presentation

- The patient is a 19-year-old healthy female, gravida 1 para 0 who presented at 12 weeks EGA for ultrasound evaluation. anatomy via ultrasound. The examination was normal.
- NIPT was LOW RISK for fetal aneuploidy, with a 5.4% fetal fraction, male sex predicted, low risk for 22q11.2 microdeletion. POSITIVE gene carrier screen for cystic fibrosis gene mutation, low risk for fetal CF disease. MS-AFP was ELEVATED, 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 (figure 2), 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 (figure 1).



Figure 1. Karyotype of fetal trisomy 9. ¹

- The patient's course was significant for worsening IUGR and additional structural abnormalities including micrognathia, abnormal posturing of the hands and rocker bottom feet.
- At 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. An uncomplicated induction of labor followed, with misoprostol, cervical balloon, and oxytocin Rx. The patient had a breech delivery of a male neonate, weight 797 g. Multiple neonatal dysmorphic features were noted at delivery.
- The placenta was notable for 3rd percentile weight for GA, mild to moderate microcalcifications and a three-vessel umbilical cord.
- The patient was discharged home the following day in stable condition.

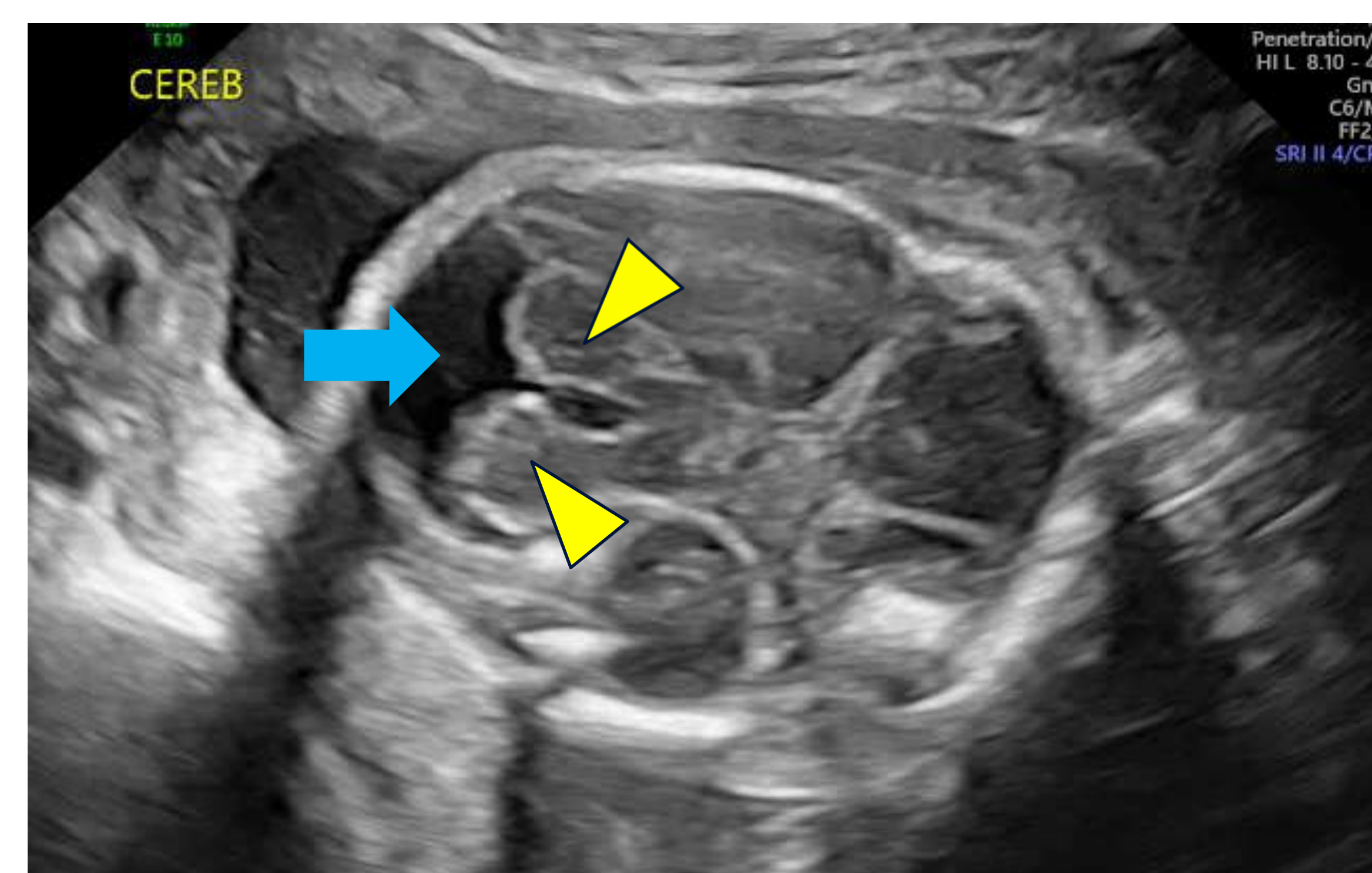


Figure 2. Splayed cerebellum (▲) and posterior fossa cyst (↑), seen in Dandy-Walker malformation.

Discussion

In this case, LOW RISK NIPT was insufficient to detect a lethal fetal trisomy leading to amniocentesis for confirmation. Existing literature aligns with the belief that rare trisomies are most difficult to screen for with NIPT, and that invasive testing should be performed if a rare trisomy is suspected.¹ In this case, ultrasound screening prompted the recommendation for amniocentesis, ultimately providing the diagnosis of trisomy 9. Given the grim prognosis, the patient opted for conservative management rather than heroic intervention.

Conclusion

- NIPT failure is a relatively common result, occurring 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 gestation, maternal obesity, triploidy and confined placental mosaicism.
- Our patient had no significant risk factors for a false negative NIPT.
- An “insufficient” or “non-reportable” NIPT result is associated with fetal aneuploidy and should lead to level 2 ultrasound and genetic counseling. Genetic amniocentesis is warranted in the setting of fetal sonographic “markers” of aneuploidy, IUGR or for patient reassurance.
- Ultrasound is an indispensable screening modality for the detection of fetal aneuploidy.

References

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