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CASE REPORT

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Placental Mosaicism in the Era of Cell-Free DNA (cfDNA) Screening: A Case Report and Review of the Literature

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Abstract

Cell-free DNA (cfDNA) is a high-performance screening test reporting fetal trisomies 13, 18, and 21. Although the sensitivity and specificity of cfDNA are superior to traditional screening tests, false-positive results are expected and may even be more likely than true positive results depending on a patient's age.

A 41-year-old gravida 2 para 1 whose cfDNA screening was positive for trisomy 13 was seeking confirmatory testing. Chorionic villus sampling (CVS) at 13 weeks' gestation demonstrated trisomy 13, however an early anatomic survey was normal. She desired pregnancy termination only if other etiologies for an abnormal cfDNA had been excluded. A detailed ultrasound at 16 weeks' gestation was normal. Amniocentesis immediately followed and demonstrated a normal fetal karyotype (46, XX). She delivered a healthy infant at 37 weeks, postnatal karyotype was 46, XX, and placental pathology was consistent with confined placental mosaicism which was without other pregnancy complications.

CVS and cfDNA results are based upon the same placental tissues, and in the setting of a normal early anatomic ultrasound, CVS may not be the preferred diagnostic test following cfDNA based upon patient preferences.

Keywords: *placental mosaicism; cell-free DNA (cfDNA); chorionic villus sampling (CVS); amniocentesis; aneuploidy*

Background

Screening for fetal aneuploidy during pregnancy using cfDNA has increased dramatically since the technology first became commercially available [1]. Many trials demonstrate high sensitivity and specificity of this screening test, estimated respectively at 99.3% and 99.9% for trisomy 21, 97.4% and 99.8% for trisomy 18, and 91.6% and 99.9% for trisomy 13 [1-3]. The positive predictive value (PPV) for a given aneuploidy is limited by low prevalence and is most influenced by patient age, therefore leading to a low positive predictive value. The low predictive value of cfDNA for trisomy 13 is most striking because it is less commonly encountered than trisomies 18 or 21: the PPV for a 25-year-old patient is 9%, while it increases to 57% for a 40-year-old patient [3].

Despite the superior sensitivity and specificity of cfDNA compared to traditional hormonal-based maternal serum screening, positive test results require a confirmatory diagnostic test. False-positive results may be caused by events such as a co-twin demise [4], maternal chromosome abnormalities [5,6], or maternal malignancy [7-9]. More recently, placental mosaicism is a known cause which may lead to positive cfDNA testing that is not concordant with final fetal karyotype [1,10]. Understanding all potential causes of a positive cfDNA result is mandatory for providing appropriate genetic counseling. Given the ethical and medicolegal considerations involved, informing patients of cfDNA screening limitations (false-positive, false-negative, and non-reportable results) is a critical aspect of this counseling. Moreover, it is important to counsel patients on the diagnostic limitations regarding CVS when attempting to confirm a cfDNA test result because both tests rely upon placentally-derived tissues. While not available until later gestational ages, amniocentesis maintains the advantage of testing actual fetal-derived cells within amniotic fluid.

Case

A 41-year-old gravida 2 para 1 desired non-invasive aneuploidy screening and underwent cell free DNA (cfDNA) using QNatalTM Advanced cfDNA screening test (Quest Diagnostics, Secaucus, NJ) at 10 weeks' gestation. The cfDNA screening test, which uses circulating DNA from placental cytotrophoblast as a surrogate for fetal DNA, was consistent with trisomy 13. She was referred to our center at 13 weeks' gestation and met with a genetic counselor. First trimester anatomic evaluation did not identify any anomalies to help corroborate the cfDNA results. She opted for diagnostic testing with chorionic villus sampling (CVS). Interphase fluorescence in situ hybridization (FISH) and karyotype of cultured mesenchymal cells demonstrated trisomy 13, consistent with the initial cfDNA screening test. Due to the normal first trimester anatomic survey and counseling regarding the limitations to differentiate between placental mosaicism and a true positive trisomy 13 result in her fetus, the patient desired amniocentesis. A detailed ultrasound at 16 weeks' gestation did not identify any structural abnormalities or soft markers for aneuploidy. After this ultrasound, she underwent an amniocentesis, which showed normal interphase FISH and karyotype of cultured amniocytes (46, XX). She was counseled that the most likely explanation for the discordant results between the cfDNA and CVS versus amniocentesis was confined placental

mosaicism. The patient continued the pregnancy which was not complicated further in the setting of confined placental mosaicism. She delivered a healthy female infant at 37 weeks' gestation. The infant was admitted to the newborn nursery and discharged home on hospital day two. Postnatal karyotype on neonatal blood was normal (46, XX).

Conclusion

Invasive prenatal diagnosis is necessary to confirm a positive cfDNA test prior to termination of pregnancy as per American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine guidelines [3]. Despite the exceedingly high performance of cfDNA for trisomies, false-positive testing is common with trisomy 13 given a low prevalence even with advanced maternal age. For trisomy 18, nearly two false-positive results are expected per accurate cfDNA test result, and for trisomy 13 the expected false-positive to true-positive rate is approximately one to one [11]. Given the potential for confined placental mosaicism, CVS may not be the best confirmatory test for all patients with cfDNA positive for trisomy 13 who do not have corroborative ultrasound findings and are considering pregnancy termination. Detailed fetal ultrasound and fetal echocardiogram represent additional options to look for typical anatomical defects to assist in making an early diagnosis. In a desired pregnancy, skepticism of trisomy 13 diagnosis should be maintained in the setting of normal fetal anatomy.

After positive cfDNA, CVS is the earliest available confirmatory diagnostic test recommended prior to pursuit of pregnancy termination for trisomy. Genetic counseling should include the discussion of reasons for positive results including true fetal karyotype, as well as false positives due to conditions such as confined placental mosaicism. In the setting of normal fetal ultrasound and abnormal cfDNA, it is important to consider placental mosaicism as a cause of misdiagnosis. Finally, as in the case of the patient presented, amniocentesis was the superior test of choice given the unacceptability of pregnancy termination for this patient in the setting of placental mosaicism. Early anatomic survey may strengthen the diagnostic yield of CVS prior to pregnancy termination for trisomy 13 [12].

Conflict of Interest Statement

All authors together report no intellectual, financial, or positional conflicts of interest related to the proposed manuscript.

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