Title:

Low incidence of abnormal cell free fetal DNA testing in the presence of isolated sonographic soft markers for aneuploidy

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Description:

Introduction: Sonographically detected fetal anomalies increase the risk for fetal chromosomal abnormalities and are a common indication for offering prenatal genetic testing. Most women undergo an anatomy sonogram at 18-21 weeks gestation, during which soft markers can be detected. These are known to be associated with an increased risk for fetal aneuploidy, but can also be present in otherwise healthy fetuses. Soft markers are combined with other factors such as maternal age and serum marker screening results to calculate a risk estimate for aneuploidy, which may lead to offering invasive diagnostic testing. Yet, women often decline such testing to avoid the small risk for miscarriage associated with the diagnostic procedure and opt instead for cell-free fetal DNA (cffDNA) screening, which has high sensitivity and specificity for common aneuploidies. Soft markers have been well demonstrated to be associated with Trisomy 21 and Trisomy 18, each having established likelihood ratios available for risk estimation of these two conditions. We sought to determine at our center how often cffDNA screening was abnormal for Trisomy 21 or Trisomy 18 when there were one or more isolated soft marker(s) found on ultrasound in the absence of other structural fetal abnormalities.

Methods and Material: Retrospective analysis of medical records was performed under an approved retrospective human subject research protocol with waiver of consent for patients seen for reproductive genetic counseling at a large tertiary care center between 07/01/13 and 4/30/15. For this study, we included data on women who completed cffDNA testing following identification of one or more isolated soft markers for fetal aneuploidy on

their second trimester anatomical survey sonogram, and women who had cffDNA testing for another indication, such as advanced maternal age, but were subsequently found to have one or more isolated soft markers. “Soft markers” were defined based on previous literature and included echogenic intracardiac focus (EIF), choroid plexus cyst (CPC), increased nuchal fold thickness > 6 mm, mild renal pyelectasis, mild ventriculomegaly, single umbilical artery, absent nasal bone, echogenic bowel, and short femur/humerus. “Isolated” was defined by the presence of one or more soft markers in the absence of a major structural abnormality. This study did not differentiate which type of cffDNA screening patients had, and only a small subset included microdeletion analysis.

Results: We identified 1,742 women who had cffDNA screening ordered during the study period. Of these 221 were in association with isolated soft markers for fetal aneuploidy. Two patients did not complete cffDNA screening and were excluded from analysis. Of the 219 who completed the cffDNA screening, 214 (97.72%) were screen negative, 2 (0.91%) were screen positive, both for Trisomy 21, and 1 (0.46%) was reported by laboratory parameters as “borderline abnormal” for Trisomy 21. A false positive rate for this cohort cannot be determined, as amniocentesis was declined in these cases. Additionally, 2 (0.91%) were abnormal for incidental chromosome abnormalities: a 22q11.2 deletion was detected in a fetus with an echogenic bowel, and XXY was detected in a fetus with an EIF. Both of these were confirmed as true positives on amniocentesis.

Conclusion: Sonographic findings associated with an increased risk for aneuploidy are an instance in which cffDNA testing is considered an option for patients who decline invasive diagnostic testing following genetic counseling about their increased risk for fetal aneuploidy. Based on this relatively small series, there is a <1% chance for cffDNA to be abnormal when isolated soft markers for aneuploidy are found on the fetal sonogram. Further investigations are needed to clarify the utility of cffDNA testing when one or more isolated soft markers for aneuploidy are present with no additional high-risk indications.

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Noninvasive prenatal diagnosis/screening

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