CfDNA testing and risk of fetal aneuploidy in cases with failed results due to low fetal fraction

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Objective

To assess the frequency of fetal chromosome abnormalities in women who undergo non-invasive prenatal screening based on cell-free DNA (cfDNA), but fail to receive a result due to low fetal fraction (FF); and to identify the subset of women who are at highest risk and would most benefit from immediate referral for ultrasound evaluation and/or diagnostic testing.

Methods

Pregnancy outcome information was sought for a cohort study of 1,350 women who received a “no-call” result due to low FF. A model was developed that incorporated prior risk (based on maternal age and prevalence of triploidy) with maternal weight and gestational age adjusted fetal fraction, to modify the risk for chromosome abnormality. A cut-off of ≥1/100 was used to define those women considered to have a high fetal–fraction-based risk (FFBR) for triploidy, trisomy 18 (T18), or trisomy 13 (T13).

Results

The 1350 cases included 1011 (75%) with normal fetal karyotypes, 21 (1.6%) with triploidy, 11 (0.8%) with T18, 3 (0.2%) with T13, and 13 (1.0%) with other aneuploidy (including T21 and monosomy-X). An additional 9 (0.7%) cases had suspected chromosome abnormalities (based on an unconfirmed second NIPS result). There were also 100 (7.4%) pregnancies that ended in fetal death with normal or unknown karyotype. 195 (14.4%) cases were lost to follow-up and were removed from the following calculations, along with 7 cases removed due to missing information such as maternal weight. The observed number of T21 pregnancies (n=8, 0.7%) was not significantly higher than the number expected based on age alone (n=8.6, 0.7%). The FFBR algorithm identified 564 (49%) of cases as high-risk and within this sub-group; 40 (7.1%) had a confirmed chromosome abnormality and 83 (14.7%) experienced fetal death with normal or unknown karyotype. Within the remaining 584 (51%) with low FFBR, 8 (1.4%) had a confirmed chromosomal abnormality and 16 (2.7%) experienced fetal death with normal or unknown karyotype. These latter frequencies appeared to be similar to those expected for the general NIPT referral population.

Conclusion

Low FF is associated with a high risk for fetal death, triploidy, T18, and T13, but not T21. The FFBR algorithm identified a high-risk sub-group that should be immediately referred for ultrasound and additional testing. Repeat NIPS or alternative screening could be considered for the FFBR low risk group in the absence of other risk factors. Measurement and reporting of FF is an essential component of NIPS.