Maternal cell-free DNA (cfDNA) sequencing versus standard prenatal aneuploidy screening in a general obstetrical population

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Objective

In high-risk pregnant women, noninvasive prenatal testing using massively parallel sequencing of maternal plasma cell-free DNA (cfDNA) accurately detects fetal aneuploidy but this performance in low-risk women is unclear. The primary objective of the Comparison of Aneuploidy Risk Evaluation (CARE) study was to compare the false positive rates of cfDNA sequencing versus standard prenatal aneuploidy screening for trisomy 21 and trisomy 18. The secondary objective was to examine the performance of the test for trisomy 13 if standard screening results were available.

Methods

At 21 US centers, blood samples were collected from pregnant women with singleton gestations from 8 weeks who were undergoing standard aneuploidy screening (serum biochemical assays with or without nuchal translucency measurement). We performed massively parallel sequencing in a blinded fashion to determine the chromosome dosage for each sample. Birth outcomes or karyotypes were the reference standard.

Results

The analysis cohort included 1914 women (mean age, 29. 6 years) with an eligible sample, a singleton euploid fetus, results from cfDNA testing, and a risk classification based on standard screening. For trisomies 21 and 18, the false positive rates with cfDNA testing were significantly lower than those with standard screening (0. 3% vs. 3. 6% for trisomy 21, P<0. 001; and 0. 2% vs. 0. 6% for trisomy 18, P = 0. 03). There was a trend (p=0. 059) toward significant improvement in false positive rate for trisomy 13 in 899 patients with risk classification by standard screening. cfDNA testing detected all cases of aneuploidy (5 for trisomy 21, 2 for trisomy 18, and 1 for trisomy 13; negative predictive value, 100% [95% confidence interval, 99. 8 to 100]). The positive predictive values for cfDNA testing versus standard screening were 45. 5% versus 4. 2% for trisomy 21 and 40. 0% versus 8. 3% for trisomy 18.

Conclusion

In a general obstetrical population, cfDNA prenatal testing had significantly lower false positive rates for detection of trisomies 21 and 18 than current forms of standard screening. There was an improvement by a factor of 10 in the positive predictive value for trisomy 21 in this predominantly low-risk patient population. The findings, suggest that cfDNA testing merits serious consideration as a primary screening method for fetal autosomal aneuploidy.