The clinical utility of genome-wide non-invasive prenatal screening

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Objective

Conventional cell-free fetal DNA (cfDNA)-based non-invasive prenatal testing (NIPT) focuses on the detection of common aneuploidies, leaving a gap of ~17% of clinically relevant chromosomal abnormalities that would go undetected. Genome-wide NIPT would greatly expand the range of chromosomal rearrangements detectable, but it could lead to a decrease of the specificity and, consequentially, to an increase in unnecessary invasive testing. In this study, we expanded conventional cfDNA-based NIPT to cover the entire genome. We aimed to compare the performance of the two tests in a large general population of pregnant women, in order to assess the clinical utility of the genome-wide screening.

Methods

From December 2015 through May 2016, genome-wide cfDNA testing was offered to 12.114 pregnant women undergoing conventional cfDNA-based NIPT for common fetal aneuploidy. Sequencing data were analysed using two algorithms; one for common fetal aneuploidies and the second optimized to identify aneuploidies and subchromosomal aberrations.

Results

Clinically relevant chromosomal abnormalities were detected in 196 (1.6%) pregnancies and confirmed by metaphase karyotyping or array-CGH following invasive prenatal diagnosis in 169 (1.4%) cases, 151 of which involved common aneuploidies, 10 were rare autosomal trisomies and 8 were segmental imbalances. Of these, 12 were potentially viable clinically relevant chromosomal abnormalities, which would have remained overlooked if only conventional NIPT had been performed. This resulted in a statistically significant higher sensitivity (100% vs 92.64%, $p < 0.001$) than did standard screening. This was achieved without sacrificing the specificity of the test, that resulted similar to that obtained with standard cfDNA testing (99.87% vs 99.77%,$p=0.064$).

Conclusion

Genome-wide cfDNA analysis represents an enhanced screening tool for prenatal detection of chromosomal abnormalities, allowing identification of clinically relevant imbalances that are not detectable by conventional cfDNA testing. The results of this study demonstrate the clinical utility of genome-wide cfDNA analysis. This level of screening provides a significant higher sensitivity compared to standard screening while maintaining a high specificity. Such additional data has important clinical implications and may be helpful in improving pregnancy management.