DNA Sequencing: A New Era for Prenatal Aneuploidy Screening?

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BACKGROUND

Prenatal testing is commonly conducted to determine fetal autosomal aneuploidy in high risk women. The standard screening method in the first trimester involves biochemical assays including, beta human chorionic gonadotropin (hCG) and pregnancy associated plasma protein A (PAPP-A) coupled with ultrasound assessment of fetal nuchal translucency. A combination of beta-hCG, maternal serum alpha fetoprotein (msAFP), estriol and inhibin A constitutes the second trimester screening markers. Cell free DNA (cfDNA) sequencing is a new technique that involves detection of fetal DNA shed by the placenta in the maternal circulation. In contrast to the standard techniques which rely on surrogate markers, this new technique is unique as it involves non-invasive detection of a marker directly involved in the pathogenesis.

WHY WAS THE STUDY CONDUCTED?

Several studies have shown the high sensitivity and specificity of cfDNA in the detection of fetal autosomal aneuploidy. However, these studies had limited generalizability because of enrollment of women at high risk of chromosomal anomalies. Furthermore, the standard screening methods have been modified in the recent years. This necessitated a randomized controlled study involving the comparison of standard screening versus cfDNA in low risk women.

THE STUDY

The study enrolled 1914 women (mean age 29.4 years) with singleton pregnancy from 21 centers in US. The standard screening was used as a "control" compared with the sequencing for chromosomal dosage. The primary outcome was the false positive rates of trisomy 21(Down's syndrome) or trisomy 18 (Edward's syndrome) compared with the karyotype assessment or birth outcome as the reference.

The study found significantly lower false positive rates (0.3% versus 3.6% in trisomy 21 and 0.2% versus 0.6% in trisomy 18) with the cfDNA screening compared with the standard method ($p<0.001$ for trisomy 21 and 0.03 for trisomy 18). Similarly, the positive predictive value was much higher with the use of cfDNA versus standard screening (45.5% and 40% versus 4.2% and 8.3% for trisomy 21 and 18 respectively).

WHAT ARE THE STRENGTHS AND LIMITATIONS OF THE STUDY?

This study is the first randomized controlled trial to demonstrate the high sensitivity, specificity, positive and negative predictive value of cfDNA assessment when compared with the standard screening for women with low risk of fetal aneuploidy. The very high negative predictive value (99.8%) virtually eliminates the need to perform an invasive procedure for detecting the chromosomal anomaly when the test result is negative.

A major limitation of this study, that limits its clinical applicability, is that the results are underpowered to compare the detection rates and did not consider the false negative rates. Only 5 patients were found to have trisomy 21 and three to have trisomy 18. This has prompted the Society of Maternal -Fetal Medicine (SMFM) to issue a press release stating that the current evidence is not enough to alter the prenatal screening guidelines of American Congress of Obstetricians and Gynecologists (ACOG).

Another limitation of this study is that although the positive predictive value of cfDNA assessment is significantly greater than the standard method, it is fairly low overall (less than 50% for both trisomy 21 and 18). This means that the majority of the women who test positive will eventually turn out to be negative after an invasive procedure. Additionally, 28.5% measurements of cfDNA were made in the third trimester. The levels of cfDNA rise with the duration of pregnancy, thus measurement during the third trimester might have overestimated the benefit of cfDNA assessment.

While this is a significant and important step in the right direction, larger studies adequately powered for detection are needed to validate the findings before cfDNA screening for antenatal detection of fetal aneuploidy can be clinically implemented.