Determining Pregnancy Complication Risks Associated with Abnormal and Inconclusive Genome-wide Noninvasive Prenatal Testing

OBJECTIVE

The objective of this study is to determine whether patients with abnormal or inconclusive genome-wide noninvasive prenatal test (NIPT) results are at a higher risk for maternal and neonatal complications when compared to patients with normal NIPT results (control). NIPT extracts cell-free fetal DNA from maternal plasma to analyze for fetal karyotypic abnormalities. This fetal DNA originates from placental cytotrophoblasts. Although genome-wide NIPT reports high sensitivity and specificity rates for fetal aneuploidy, approximately 3-4% of these NIPT results are inconclusive and non-reportable due to either technical or biological failure (e.g. low fetal fraction in maternal serum). Low fetal fraction and inconclusive results of conventional NIPT have been associated with an increased risk of pregnancy complications, preeclampsia and fetal growth restriction when compared to the general obstetric population. Because NIPT analyzes cell-free fetal DNA of placental origin and factors that contribute to the development of preeclampsia and other adverse pregnancy outcomes are often placenta-mediated, it is proposed that abnormal or inconclusive NIPT results produce or represent a biologically plausible alteration in placental function.

MATERIALS AND METHODS

A single center retrospective study of pregnancy outcomes in patients who received a standard laboratory genome-wide NIPT test (MaterniT™ GENOME, Integrated Genetics) for fetal aneuploidy between November 2015 and September 2018. This test became available for clinical use at the inception of this study and a total of 2326 GENOME tests were performed during the study time frame. Study groups included “abnormal,” “inconclusive,” “non-negative” (abnormal + inconclusive) and a control group of patients with “negative” (normal) NIPT results. NIPT results and pregnancy outcomes were analyzed to determine whether there was an association between the individual and combined non-negative NIPT results and increased risk of perinatal and neonatal complications. Variables of interest include fetal fraction, fetal anomalies, placental anomalies, antenatal complications, preeclampsia, gestational age at delivery, fetal intrauterine growth restriction, APGAR scores, and neonatal complications. Pearson Chi square and two-tailed t-tests were performed comparing the abnormal, inconclusive, non-negative and control groups.

RESULTS

39 abnormal, 57 inconclusive and 155 controls were included in the analysis. The non-negative NIPT cohort of 96 patients (abnormal + inconclusive results) had significantly increased weight, maternal age, chronic hypertension and history of multiple spontaneous abortions when compared to the control group. Non-negative results were associated with greater risks for antenatal complications (46.9% vs. 23.9%, $p < 0.001$), preeclampsia (18.8% vs. 9.0%, $p = 0.025$), preterm delivery (34.1% vs. 14.0%, $p < 0.001$), neonatal complications (40.0% vs. 15.3%, $p < 0.001$) and NICU admission (45.2% vs. 18.0%, $p < 0.001$). Non-negative NIPT results were also associated with earlier gestational age at delivery, lower APGAR scores, and lower birth weight. When analyzed separately, inconclusive NIPT results were independently associated with preeclampsia (22.8% vs. 9.0%, $p = 0.029$), antenatal complications (45.6% vs. 23.9%, $p < 0.001$), preterm delivery (33.3% vs. 14.0%, $p <0.001$) and neonatal complications (35.3% vs. 15.3%, $p < 0.001$).

CONCLUSION

Women who have either abnormal or non-reportable genome-wide NIPT results are at greater risk for perinatal and neonatal complications when compared to women who receive a normal NIPT result during pregnancy. Non-reportable results may be a proxy for placental dysfunction at a molecular level. These patients should be monitored for the development of adverse perinatal outcomes including preeclampsia, fetal IUGR and preterm delivery. The potential risks for neonatal complications and NICU admission should be reviewed with these high-risk patients in advance of delivery. Pre-delivery neonatology consultations may be considered.