Residual risk for clinically significant copy number variants in low-risk pregnancies with a normal noninvasive prenatal screening result: does it have clinical value?

TO THE EDITORS: The introduction of noninvasive prenatal screening (NIPS) has had a tremendous impact on prenatal care. Its near-diagnostic accuracy for the detection of trisomy 21 has been reported in numerous series, and now, genome-wide NIPS modalities for targeted copy number variations (CNVs) or all CNVs in the whole genome (usually ≥7 Mb) have also become commercially available in many centers.1 For low-risk pregnancies, the universal use of NIPS will result in a dramatic increase in the diagnoses of fetal chromosomal abnormalities because of its high detection rate (DR). For high-risk pregnancies, eg, women with positive serum screening or an advanced maternal age (AMA), NIPS has led to a marked decrease in the number of invasive procedures because of its extremely low false positive rate (FPR). At present, NIPS is not recommended to patients with fetal structural anomalies, including increased nuchal translucency (NT).2,3

In a recent study, Maya et al calculated the residual risk for clinically significant CNVs following theoretically normal NIPS.4 This retrospective cohort study was based on the database of chromosome microarray analysis (CMA) at an Israeli genetic laboratory during a 9-year period. A total of 7235 low-risk pregnancies (with NT < 3 mm, normal anatomic survey, and normal maternal serum screening) were included; of these, clinically significant CNVs were demonstrated in 87 cases (1.2%). The authors assumed that the residual risk following theoretically normal genome-wide NIPS results was 0.68%, ranging from 0.82% for the AMA cohort to 0.50% in younger women. They concluded that their results of the models examining the residual CNV risk are important for women considering NIPS vs invasive testing during their pregnancy. However, this study raises some important issues that should be addressed.

All of the 7235 cases recruited had normal first-trimester NT and normal second-trimester anatomic scan and serum aneuploidy screening. So why were those women offered genetic amniocentesis? Could the indication of invasive testing be parental anxiety, or could prenatal diagnosis be required by the patients themselves even without an objective indication? Indeed, explaining the residual CNV risk in a low-risk pregnant population only has limited value in clinical practice. For these women, clinicians should provide the option of NIPS regardless of serum screening, emphasizing the higher DR compared with traditional screening approaches. This is because they have no indications for invasive testing with CMA. Only for those who have a high risk for aneuploidies, the residual CNV risk should be discussed when patients decline a diagnostic test and opt for NIPS (Figure).

Qi Tian, BSc
Prenatal Diagnosis Unit
The Third Affiliated Hospital
Sun Yat-sen University
Guangzhou, China

Dong-Zhi Li, MD, PhD
Prenatal Diagnostic Center
Guangzhou Women and Children’s Medical Center
Jinsui Rd. 9, Zhujiang New Town
Guangzhou 510623
Guangdong, China
drlidongzhi2014@sina.com

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