Clinical utility of noninvasive prenatal screening for pathogenic copy number variants

Check for updates

TO THE EDITORS: Chau et al[1] investigated the spectrum and characteristics of pathogenic copy number variants (pCNVs) in prenatal genetic diagnosis. In 23,865 fetuses for any indication for invasive testing, they found that 375 (1.6%) carried pCNVs. Of 428 pCNVs detected, 360 (84.1%) were <5 Mb in size and 68 (15.9%) were between 5 and 10 Mb.

Based on these findings and that standard noninvasive prenatal screening (NIPS) cannot reliably detect abnormalities less than 5 Mb in size, the authors concluded that pCNVs screening with NIPS should be carefully evaluated before implementing in clinical practice. However, this study raises some questions that are to be addressed.

We agree that NIPS will miss the majority of pCNVs if it is attempted in high-risk patients, and invasive testing with chromosomal microarray analysis is the preferable one for these patients. However, it should be emphasized that the ideal targeted population of NIPS is not the women at high risk, although at present NIPS behaves as a second-tier approach because of its relatively high cost as a screening test.

In their study, 375 cases were detected to have pCNVs. What is the number of background population then? The prevalence of pCNVs is 1.6% in this study, consistent with that in a high-risk population (ie, high-risk fetal aneuploidy screening results) without abnormal fetal ultrasound findings.[2] So we can make a rough calculation that the number of background population is 468,750 (assuming a false-positive rate of 5% for aneuploidy screening: $468{,}750 \times 5\% \times 1.6\% = 375$). If this is the case, we then had missed approximately 4450 pregnancies with a pCNV fetus (assuming the pCNV frequency of 1% in low-risk population: $468{,}750 \times 95\% \times 1\% = 4450$).

Collectively, microdeletion/microduplication syndromes account for 1−2% of all structurally normal pregnancies, regardless of maternal age.[3] In younger women, the risk for a clinically significant deletion exceeds the risk for Down syndrome. Therefore, chromosomal microarray analysis is recommended to be offered to all women who undergo diagnostic testing. However, for most of the women who have no indications for an invasive procedure, no routine methods are available for pCNV screening.

The NIPS provides the chance of detecting pCNVs in these women at so-called low risk.[4] For instance, if we use expanded NIPS in the previously mentioned 468,750 women, more pCNV-positive fetuses would be detected (Table 1). We believe that it is mainly the cost, rather than pCNV size, that determines the application of NIPS as a pCNV screening tool in general population.

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

The authors report no conflict of interest.

REFERENCES

1. Chau MHK, Cao Y, Yvonne Kwok KY, et al. Characteristics and mode of inheritance of pathogenic copy number variants in prenatal diagnosis. Am J Obstet Gynecol 2019;221:493.e1–11.
2. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med 2012;367:2175–84.
3. Srebniak MI, Knapen MFCM, Polak M, et al. The influence of SNP-based chromosomal microarray and NIPT on the diagnostic yield in 10,000 fetuses with and without fetal ultrasound anomalies. Hum Mutat 2017;38:880–8.
4. Liang D, Cram DS, Tan H, et al. Clinical utility of noninvasive prenatal screening for expanded chromosome disease syndromes. Genet Med 2019, on press.

 https://doi.org/10.1016/j.ajog.2019.08.030

TABLE 1
Comparison of the pCNV detection between using 2 screening tests in general population[a]

Variables	Total pregnancies, n	Pregnancies with common trisomies, n	Pregnancies with pCNVs, n	Pregnancies screened positive, n		Pregnancies with confirming diagnosis, n	
				Common trisomies	pCNVs	Common trisomies	pCNVs
cFTS[b]	468,750	468	4687	23,437	—	421	375
NIPS[c]	468,750	468	4687	2806	4686	463	2343

cFTS, combined first-trimester screening; *NIPS*, noninvasive prenatal screening; *pCNV*, pathogenic copy number variant.

[a] Assuming that the prevalence of common trisomies and pCNVs is 1 per 1000 and 1 per 100, respectively, in general population; [b] Assuming that the detection rate for common trisomies is 90% with a false-positive rate of 5% and that the prevalence of pCNVs is 1.6% in those with positive screening results; [c] Assuming that the detection rates for common trisomies and pCNVs are 99% and 50%, respectively, with a false-positive rate of 0.5% for both common trisomies and CNVs.

Xu. Clinical utility of noninvasive prenatal screening. Am J Obstet Gynecol 2019.