Is prenatal cytogenetic diagnosis with genomic array indicated in pregnancies at risk for a molecular or metabolic disorder?

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Traditionally, many laboratories (including ours) have performed cytogenetic testing by karyotyping in samples referred for invasive molecular or biochemical testing; however, these patients did not have an increased risk for chromosome aberrations. The reason for testing was to exclude the presence of microscopically visible chromosome aberrations in fetal material that was already available so that these patients could additionally be reassured. A few years ago, several laboratories introduced rapid aneuploidy testing for detection of trisomy 13, 18, and 21, triploidy, and aneuploidy of sex chromosomes as a standalone test for molecular and metabolic referrals.^{1,2} Recent advances in microarray testing in pregnancies without ultrasound anomalies led to new insights into the prevalence of submicroscopic chromosome aberrations in such fetuses. Some large-scale studies showed a significant percentage (0.5%) of pathogenic submicroscopic findings in pregnancies tested due to advanced maternal age or abnormal first-trimester screening.^{3–5} This figure excludes cases of susceptibility loci (SL), which are phenotypically heterogeneous and have a reduced penetrance.

Our recently published data⁵ were consistent with those in prior publications; 0.5% of fetuses had a pathogenic submicroscopic variation associated with an early-onset disorder, and 0.2% of fetuses had a microscopically visible aberration resulting in an abnormal fetal phenotype. Therefore, fetuses without ultrasound anomalies have a background population risk of 1 in 150 (0.7%) for an unbalanced chromosome aberration (either microscopically visible or submicroscopic) associated with an early-onset disorder. Based on these figures we concluded that, from the diagnostic point of view, array testing is the preferred cytogenetic technique to investigate the chromosomal status of the fetus in all invasively sampled cases.⁶ However, it is interesting to note that invasive sampling due to a risk of aneuploidy followed by karyotyping has been commonly accepted,⁷ but there are debates and no consensus on offering extra genomic array testing owing to a population risk of approximately 1 in

150 for a segmental imbalance in pregnancies that have already been sampled for other (molecular or biochemical) reasons.⁸

Our previous study evaluated the frequency of microscopic and submicroscopic copy-number variations in patients presenting for prenatal diagnostic testing for a variety of indications.⁵ To evaluate the utility of array testing in patients with no risk factors for karyotypic abnormalities, we reanalyzed the data. We were especially interested in whether the risk of 1 in 150 for an unbalanced chromosome aberration also applies to pregnancies referred for molecular or biochemical testing that are not at increased risk for a cytogenetic abnormality. From July 2012 to September 2014 we tested 148 pregnancies only at risk for a biochemical or a molecular disorder or referred due to maternal anxiety with 0.5Mb SNP array. In three out of 148 (2%) of the cases unexpected unbalanced chromosome aberrations were found: trisomy 21 and two submicroscopic pathogenic findings (a 1.7Mb 7q11.23 microdeletion associated with Williams–Beuren syndrome and a 3.14Mb 1q21.1 microdeletion (including the TAR region and distal 1q21.1 microdeletion), a SL for neurodevelopmental disorders and also associated with an increased risk for cardiac malformations). These results are consistent with our previous estimate⁵ and show that two out of three imbalances would not be diagnosed by both rapid aneuploidy testing and karyotyping, justifying the use of the array technique for cytogenetic studies in these pregnancies.

In conclusion, because pregnant women and their partners wish to make their own choices about the scope of prenatal diagnosis,⁹ we believe that patients referred for invasive testing due to a molecular or biochemical disorder should additionally receive comprehensive pretest counseling about their risk for an unbalanced chromosome aberration—not only the individual risk for a common aneuploidy but also their background population risk of approximately 1 in 150 for an early-onset disorder caused by a (submicroscopic) chromosome aberration. In these pregnancies, the miscarriage risk due to the invasive procedure has already been taken. Only when all testing options

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are discussed can personalized informed choices regarding prenatal testing be made.

DISCLOSURE

The authors declare no conflict of interest.

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