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Editorial

Detection of chromosome abnormalities: Beyond conventional karyotyping

Pregnancy loss is a gravely unhappy and emotionally stressful event for any couple. Besides having to address what may be a couple's psychosocial embarrassment due to their loss, one of the challenges for most researchers is how to identify these pregnancy loss cases with genetic defects that are destined to miscarry from other treatable cases.[1] It remains indisputable that chromosomal karyotyping is the *gold standard* for prenatal diagnosis, including pregnancy loss.[2] However, researchers can obtain virtually the same or better diagnostic information for detecting gains and losses of genetic material across the genome using microarray analysis, also known as molecular karyotyping and/or chromosomal array analysis, including array-based comparative genomic hybridization[3] and single nucleotide polymorphism (SNP) array.[2] All of these different arrays create an entire genome scanning panel. Comparative genomic hybridization is able to discover and map genomic regions for chromosomal gains or losses in a single experiment without knowledge pertaining to the locations of regions of abnormalities.[3] SNP combing across the genome (approximately 1/10 kb) with an informatics technique is used to detect gains and losses and identifies maternal cell contamination, triploidy, and uniparental disomy.[4]

In this issue, Lin et al[5] have authored an interesting article entitled *Improved assay performance of single nucleotide polymorphism array over conventional karyotyping in analyzing products of conception*. We heartily applaud the publication of this article, because the diagnoses were consistent with previous reports based on traditional cell culture and karyotyping of products of conception. In Lin et al's[5] study, approximately 64.5% (100/155) of samples were cytogenetically abnormal (including 52% single trisomy, 11% monosomy X, and 6% triploidy). SNP array not only demonstrated a higher success rate for detecting chromosomal abnormalities (98.1% vs. 85.8%), but also provided an additional ability to detect pathologic copy number variations and whole-genome uniparental disomy (UPD) compared with conventional karyotyping (G-banded karyotyping), thus contributing to a higher detection rate of abnormalities (62.6% vs. 61.3%).[5] Furthermore, the use of SNPs also significantly improved sensitivity to mosaicism.[5] By contrast, two cases of chromosome translocation and one case of tetraploidy were not detected by SNP but by conventional karyotyping.[5] The authors suggested that SNPs would be an alternative method to karyotyping in clinical genetic practice. In fact, Pergament et al[6] recently published a very intriguing report, when they studied 1064 maternal blood samples from 7 weeks of gestation and beyond using the Next-generation Aneuploidy Test Using SNPs algorithm. This study showed that the test provided results associated with a high level of sensitivity and specificity. Furthermore, Levy et al[7] reported the full cohort of identifiable anomalies, regardless of known clinical significance, in a large-scale cohort of postmiscarriage products-of-conception samples analyzed using a high-resolution SNP-based microarray platform. They concluded that using SNPs extends the scope of detectable genomic abnormalities and facilitates reporting *true* fetal results, supporting the use of SNP chromosomal microarray analysis for cytogenomic evaluation of miscarriage specimens when clinically indicated.

Although Lin et al's[5] report confirmed the validity of SNP microarray analysis, the obvious question is: when should these tests be ordered? Currently, cytogenetic evaluation of products of conception is not routinely recommended.[4] It may be that the advent of this new technology could compel us to rethink that policy and start testing this tissue more liberally. Approximately 25% of all recognized pregnancies ended in spontaneous miscarriage, with the majority caused by sporadic aneuploidy.[4] Most authorities do not believe that karyotyping products of conception after one miscarriage will be beneficial for these parents, because the result would not change treatment for the vast majority of couples and these evaluations are too expensive.[4] Although cytogenetic investigation is suggested for those parents with recurrent pregnancy loss, this recommendation applies to obtaining parental karyotypes and not the karyotype of products of conception.[8] Additionally, confirming a genetic abnormality in products of conception, resulting in a lack of further parental evaluation, could lead to failure to identify another remediable cause for miscarriage.[4] Finally, testing all products of conception might be considered for purposes of reassuring the parents. However, the basic cost of the test, coupled with the fact that 50% of the results would be euploid and could not provide an explanation for the pregnancy loss, argue against such a practice.[4]

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Other arguments associated with Lin et al's[5] article were that 10.3% of miscarriages occurred in the second trimester, which requires further discussion. Testing fetal tissue after the second or third trimester pregnancy loss might obviate the need to do additional studies, such as imaging for uterine anomalies[9] or testing for antiphospholipid antibody syndrome.[10]

Wilson et al[11] at the 18th International Society for Prenatal Diagnosis International Conference on Prenatal Diagnosis and Therapy, which was held in Brisbane, Australia on July 22, 2014, provided the final consensus summary. Namely, that while the present genomic diagnostic technology with access to prenatal testing following an informed consent process recommendation would probably become a *future* standard of care for prenatal screening/diagnosis/therapy, when specific fetal abnormalities/syndrome are identified, the debate recommendation could not be completely supported at this time by the international audience attending the 2014 18th International Society for Prenatal Diagnosis meeting in Brisbane, Australia. In summary, SNP-based microarray analysis of products of conception is likely to give accurate results for the majority of parents, however, whether and when it is appropriate to perform this analysis remains uncertain.

Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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