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COMMENT

Rare autosomal trisomies detected by non-invasive prenatal testing

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In this issue of EJOG, Lannoo et al. [1] present the results of a daunting task; a review of rare autosomal trisomies (RATs) with the goal of providing clinical guidance for women receiving genome-wide (gw) non-invasive prenatal testing (NIPT). RATs are trisomies not involving chromosomes 13, 18, 21, or sex chromosomes. Non-mosaic RATs are seen in a high proportion of first trimester spontaneous abortions. They are only rarely encountered in amniotic fluid cells and exceedingly rare in livebirths where they are only detected in a mosaic state [2]. RATs are surprisingly common in placental cells. To appreciate the challenge in assessing their clinical significance when detected through gwNIPT, it is necessary to briefly summarize current understanding of their origins and the basis for clinical concern.

Early embryos show extensive aneuploidy with strong early selection against abnormal cells. Abnormality may be of meiotic origin or arise in the zygote or in the cell generations shortly thereafter [3]. Only a few cells are destined to become the fetus and therefore the fetus will not necessarily be fully representative of all cells in a mosaic embryo. Moreover, it is likely that lineage-specific cell selection occurs during development and additional somatic cell errors may arise. This view is supported by cytogenetic studies on chorionic villus samples (CVS) where mosaic aneuploidies are occasionally encountered in cytotrophoblasts, or mesenchyme, or both, but are usually not detected in the fetus, i.e., there is a confined placental mosaicism (CPM). Those abnormalities present in both cytotrophoblasts and mesenchyme are more likely to be meiotic in origin and these are more likely to be associated with pregnancy loss [4] or low birth weight [5]. Each specific abnormality is likely to have a different effect on placental development and function. For example, trisomy 16 is associated with a cystic placenta and markedly abnormal maternal serum placenta-derived analytes which are not seen for other trisomies [6]. Further complicating the interpretation of CPM is the need to consider the consequences of uniparental disomy (UPD). Risk for an abnormal phenotype exists when the mosaicism involves a chromosome 6, 7, 11, 14, 15 or 20 due to imprinted genes. The risk for UPD is not the same for each of these chromosomes [1]. There may also be a (currently undefined) risk for abnormality for other chromosomes with UPD because of the expression of a recessive disorder associated with the reduction to homozygosity. Each specific case with placental mosaicism should therefore be viewed as having a distinct, rare, combination of the specific trisomy, the percentage of abnormal cells, cell selection, the compartmentalization of the abnormal cells into different cell lineages, and the consequences of UPD.

Current methods for NIPT are based on the analysis of cell-free DNA in maternal plasma, which is a mixture of DNA derived from trophoblasts (commonly, but erroneously, called "fetal DNA") and DNA from maternal cells [7]. The proportion of DNA that is fetal is variable and the ability to detect a minor mosaic abnormal cell line will be dependent on both the fetal fraction and the laboratory methods used (for example, the depth of sequencing). Initially, NIPT was designed to detect trisomies 21, 18 or 13, where mosaicism is relatively infrequent. The rate of false-positive tests due to CPM was acceptable and definitive diagnosis was available through CVS or amniocentesis. Performance of NIPT was less satisfactory for monosomy X, in part, because mosaicism is much more common. Use of gwNIPT, which aims to detect all large imbalances (typically, >7 Mb), opens the door to the detection of all RATs present in trophoblasts. gwNIPT can potentially detect rare large segmental imbalances although these results can also constitute false-positive findings [8].

gwNIPT does not distinguish between fetal and maternal aneuploidy (although the proportion of DNA showing the abnormality is often a clue). Maternal chromosome imbalances include those associated with cancer (including benign leiomyomas) [9]. In some cases, without additional testing, it may not be possible to distinguish between a placental/fetal and a maternal malignancy-associated RAT (for example, trisomy 8 as the sole abnormality).

Given the complexity, how can patients with a RAT be counseled? For these women, a normal CVS and amniocentesis result is not sufficiently reassuring. As Lannoo et al. [1], document, for each specific finding, there is currently considerable uncertainty about the risk for pregnancy complications. Combining available information on pregnancy complications for RAT cases ascertained through gwNIPT and cytogenetic analysis of CVS may not be correct because it assumes both technologies are equivalent with respect to the mosaic cases identified. When data is scant, prudence often dictates defaulting to high-risk clinical management, i.e., frequent ultra-sounds for growth restriction and fetal abnormality, preeclampsia monitoring, early delivery, NICU admission, etc. Some women will need to be informed about the risk for maternal malignancy. In reality, when gwNIPT was utilized by an apparently self-selected population (which could have been enriched for higher risk pregnancies), there was only modestly increased risks of pregnancy complications for RAT-positive cases compared to expected rates for the whole population (with the exception of trisomy 16) [8]. Lennoo et al. [1], note that "reporting a RAT detected by NIPT and subsequent invasive testing can only be justified if there is sufficient

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evidence that this has the potential to improve pregnancy management and outcome." They do not express an opinion on whether this requirement has been met.

Lennoo et al. [1], identify specific areas for future research. Several require assessing the level of mosaicism and correlating this with clinical outcomes. However, precise measurement of the level of mosaicism is currently not included in the design of most commercially available NIPTs. Given the previously discussed heterogeneity in RAT positive cases, and the initial data indicating only weak associations, the trials assessing clinical utility would need to be large, require unbiased case inclusion, and comprehensive information on pregnancy outcomes.

It has been pointed out that it is incumbent on the sponsors and advocates of gwNIPT to undertake these clinical trials and to only provide the clinical service once there is an unbiased evidence base and a clear pathway for patient management [10]. The currently available information for interpreting RATs identified by gwNIPT is distressingly inadequate.

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COMPETING INTERESTS

PB is a consultant and holds stock options in Natera, Inc. He is also on an Advisory Board for Menarini Biomarkers.

ADDITIONAL INFORMATION

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