Taylor & Francis
Taylor & Francis Group

Expert Review of Molecular Diagnostics

ISSN: 1473-7159 (Print) 1744-8352 (Online) Journal homepage: http://www.tandfonline.com/loi/iero20

Is carriership of a balanced translocation or inversion an indication for non-invasive prenatal testing?

Malgorzata I. Srebniak, Ida Vogel & Diane Van Opstal

To cite this article: Malgorzata I. Srebniak, Ida Vogel & Diane Van Opstal (2018): Is carriership of a balanced translocation or inversion an indication for non-invasive prenatal testing?, Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2018.1468255

To link to this article: https://doi.org/10.1080/14737159.2018.1468255

Accepted author version posted online: 20 Apr 2018.
Published online: 26 Apr 2018.

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS, 2018
https://doi.org/10.1080/14737159.2018.1468255

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Is carriership of a balanced translocation or inversion an indication for non-invasive prenatal testing?

Malgorzata I. Srebniak[a], Ida Vogel[b,c,d] and Diane Van Opstal[a]

[a]Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, The Netherlands; [b]Departments of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark; [c]Center for Prenatal Diagnostics, Aarhus University Hospital, Aarhus, Denmark; [d]Institute of Biomedicine, Aarhus University, Aarhus, Denmark

ARTICLE HISTORY Received 16 January 2018; Accepted 19 April 2018

KEYWORDS NIPT; invasive testing; indication; prenatal screening; balanced chromosome aberration carrier; prenatal

Patients who experienced recurrent miscarriages may tend to refuse invasive testing due to the procedure-related miscarriage risk, even if they are carriers of a balanced translocation. Carriers of a balanced chromosome aberration may go through multiple miscarriages of unbalanced products of conception and are very anxious about taking any risk when pregnancy survives longer than the previous ones have. In some countries in daily practice there is increasing demand for noninvasive prenatal testing (NIPT) for this indication. NIPT is indeed used as a prenatal screening technique to detect the common aneuploidies [1] and it has also been shown that subchromosomal unbalanced aberrations and even submicroscopic imbalances (microdeletions and – duplications) can be detected [2,3]. However, although several publications have demonstrated NIPT detection of deletions, currently available whole-genome tests are not extensively validated to detect deletions of particular sizes. Nevertheless, we hypothesized that NIPT could be a second-best option for carriers of balanced aberrations, who are not willing to take the 0.1%–0.2% risk of miscarriage induced by invasive testing. To be able to consider this option some questions should be answered. Could noninvasive testing serve as an early diagnostic or screening test? Is the resolution of the test good enough to detect the possible imbalance in the individual family? Can a referring clinician assess the size of the possible imbalance?

Carrying a balanced translocation or an inversion is typically an indication for invasive prenatal diagnosis using chorionic villi (CV) sampled in the first trimester of pregnancy due to the high risk for unbalanced offspring. Aneuploidy in the cytotrophoblast (or short-term cultured villi – STC-villi) does not always represent the fetal karyotype as reliably as the mesenchymal core (long term cultured villi). However, yearlong experience from cytogenetic testing of CV shows that the presence or absence of familial (un)balanced translocation can reliably be assessed in the cytotrophoblast of CV, which enables a rapid prenatal diagnosis [4–6]. Therefore, theoretically, analysis of cell free (cf) DNA of which the fetal part originates from the cytotrophoblast, should also give reliable results. When NIPT shows the unbalanced product of the parental structural chromosome aberration such a result might therefore be considered as a definitive diagnosis (in the absence of a vanishing twin). Moreover, the interpretation of such result will be easy since the translocation breakpoints are known in advance and the duplication and deletion are present at the same time at known chromosomal locations. Therefore, the performance of NIPT to detect known familial unbalanced translocations is expected to be better than detecting *de novo* structural chromosome aberrations. If another chromosome aberration is found, follow-up diagnostic testing is still necessary.

Another consideration is whether the resolution of current NIPT technology is 'good enough' to be used for subchromosomal imbalances. According to some authors, NIPT based on cfDNA already allows screening with a resolution similar to karyotyping and there are many efforts done to introduce screening for submicroscopic aberrations as well [2,7–14]. At this time point it is difficult to compare the cases presented in the literature as there is a large variety of available tests that differ in cfDNA isolation, library preparation, sequencing, data analysis, software, as well as fetal fraction measurements and gestational age. Nevertheless carriers of Robertsonian translocations that have an increased risk for a trisomic offspring have already been offered NIPT as an alternative for invasive sampling [15], as the sensitivity for detection of whole chromosome trisomy is well described [1]. Moreover, many authors show that their particular test is able to detect structural chromosome aberrations [2,7–10,13,14]. Most authors claim 4% fetal fraction as minimal for trisomy detection. However, the minimal percentage of 'fetal' cfDNA fraction necessary for reliable detection of all subchromosomal aberrations has not yet been assessed and will likely depend on the genomic size of the imbalances. Kitty K. Lo and colleagues estimated the test sensitivity for deletions of different sizes depending on the fetal fraction and sequencing depth. They concluded that to be able to detect a deletion of about 10Mb with high sensitivity, a fetal fraction of 10% and at least 10 mln reads are necessary, while detecting a 3

CONTACT Malgorzata I. Srebniak m.srebniak@erasmusmc.nl Department of Clinical Genetics, Erasmus Medical Center, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands

Mb deletion in such a sample with the same sequence depth is practically impossible [16].

When a robust test with a reliable resolution is available, the case selection by a clinician should be done carefully. To be able to advice an individual patient on whether NIPT is an option for them, the size of potential segmental imbalances should be estimated based on the translocation or inversion breakpoints. Since most of the balanced translocation carriers have been detected by conventional karyotyping, most of the imbalances would concern aberrations larger than 5–10 Mb. However, for the determination of the chromosomal breakpoints in particular families, the ones assessed by microarray on unbalanced offspring are preferred over those determined by karyotyping to decrease the risk of cryptic genomic imbalances. The individual family breakpoints should be evaluated and the sizes of potential imbalances can be assessed by using a genome browser. Roughly, the size of the distance between the chromosomal breakpoint and a telomere can be measured and in this way a clinician should be able to estimate whether a particular genome-wide NIPT test with a well-established resolution is appropriate for the individual family. For instance, if potential imbalances are expected to be >20 Mb, the freeware Wisecondor, may be an appropriate NIPT test [11].

Obviously, more research is needed to establish the ability of NIPT to detect unbalanced translocations. Preferably whole genome approaches should be employed to investigate all chromosomes. In order to fully validate a NIPT test for carriers of balanced chromosome aberrations, ideally a large cohort should be evaluated with both NIPT and invasive testing followed by microarray. It would also be interesting to clinically test whether the test resolution changes with gestational age and therefore fetal cfDNA fraction in order to determine the optimal sampling time. However, this will obviously be very difficult to accomplish in a clinical setting since only a minority continues pregnancy when the fetus is affected and multiple sampling in affected pregnancies may not always be possible. We question whether it will be necessary to validate genome-wide NIPT for all possible combinations of chromosomal imbalances in order to call this test validated for detection of subchromosomal aberrations. Neither karyotyping nor microarray were validated for all possible imbalances before they were implemented for clinical use. Ideally imbalances of all telomeric regions should be validated, but as the individual cases are rare it may not be clinically feasible to do so. To ensure a sufficient fetal fraction of cfDNA, it may be reasonable to test these pregnancies later in the pregnancy than the current test for aneuploidy is done.

Finally, in our opinion, an invasive test should be the gold standard for high risk pregnancies, but NIPT could be the second-best choice when one of the parent carries a balanced chromosome aberration and refuses invasive testing. In all cases, an appropriate pretest counseling is indispensable. It was shown that after pretest counseling, patients seem to understand the limitations of NIPT and are capable to make their own informed choices (van der Steen et al. own manuscript under review). A good counseling explaining the limitation of the particular NIPT test in relation to the medical question is mandatory to avoid false reassurance on the chromosomal status of the fetus.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. A reviewer on this manuscript works for a company that provides a NIPT product.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Gil MM, Quezada MS, Revello R, et al. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2015 Mar;45 (3):249–266. PubMed PMID: 25639627; eng.
2. Fiorentino F, Bono S, Pizzuti F, et al. The clinical utility of genome-wide non invasive prenatal screening. Prenat Diagn. 2017 Apr 17 PubMed PMID: 28423190; eng. DOI:10.1002/pd.5053.
   • **The results of this study demonstrate the clinical utility of genome-wide cfDNA analysis.**
3. Van Opstal D, van Maarle MC, Lichtenbelt K, et al. Origin and clinical relevance of chromosomal aberrations other than the common trisomies detected by genome-wide NIPS: results of the TRIDENT study. Genet Med. 2017 Oct 2. PubMed PMID: 29121006; eng.
4. Cytogenetic Analysis of Chorionic Villi for Prenatal Diagnosis: An ACC Collaborative Study of U.K. Data. Association of clinical cytogeneticists working party on chorionic villi in prenatal diagnosis. Prenat Diagn 1994 May;14(5):363–379. PubMed PMID: 8084857; eng.
5. Los FJ, van den Berg C, Van Opstal D, et al. Abnormal karyotypes in semi-direct chorionic villus preparations of women with different cytogenetic risks. Prenat Diagn. 1998 Oct;18(10):1023–1040. PubMed PMID: 9826894; eng.
6. van den Berg C, Van Opstal D, Brandenburg H, et al. Accuracy of abnormal karyotypes after the analysis of both short- and long-term culture of chorionic villi. Prenat Diagn. 2000 Dec;20 (12):956–969. PubMed PMID: 11113907; eng.
7. Zhao C, Tynan J, Ehrich M, et al. Detection of fetal subchromosomal abnormalities by sequencing circulating cell-free DNA from maternal plasma. Clin Chem. 2015 Apr;61(4):608–616. PubMed PMID: 25710461; eng.
8. Srinivasan A, Bianchi DW, Huang H, et al. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. Am J Hum Genet. 2013 Feb 07;92(2):167–176. PubMed PMID: 23313373; PubMed Central PMCID: PMC3567270; eng
9. Pescia G, Guex N, Iseli C, et al. Cell-free DNA testing of an extended range of chromosomal anomalies: clinical experience with 6,388 consecutive cases. Genet Med. 2017 Feb;19(2):169–175. PubMed PMID: 27362910; PubMed Central PMCID: PMC5303761; eng.
10. Chen S, Lau TK, Zhang C, et al. A method for noninvasive detection of fetal large deletions/duplications by low coverage massively parallel sequencing. Prenat Diagn. 2013 Jun;33(6):584–590. PubMed PMID: 23592436; eng.
11. Straver R, Sistermans EA, Holstege H, et al. WISECONDOR: detection of fetal aberrations from shallow sequencing maternal plasma based on a within-sample comparison scheme. Nucleic Acids Res. 2014 Mar;42(5):e31. PubMed PMID: 24170809; PubMed Central PMCID: PMC3950725; eng.
12. Wapner RJ, Babiarz JE, Levy B, et al. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion

syndromes. Am J Obstet Gynecol. 2015 Mar;212(3):332 e1–9. PubMed PMID: 25479548; eng.

13. Yatsenko SA, Peters DG, Saller DN, et al. Maternal cell-free DNA-based screening for fetal microdeletion and the importance of careful diagnostic follow-up. Genet Med. 2015 Oct;17 (10):836–838. PubMed PMID: 25569438; PubMed Central PMCID: PMC4496325; eng.
14. Li R, Wan J, Zhang Y, et al. Detection of fetal copy number variants by non-invasive prenatal testing for common aneuploidies. Ultrasound Obstet Gynecol. 2016;47(1):53–57; English.
15. Oepkes D, Page-Christiaens LC, Bax CJ, et al. Trial by Dutch laboratories for evaluation of non-invasive prenatal testing. Part I - clinical impact. Prenat Diagn. 2016 Oct 17 PubMed PMID: 27750376; eng. DOI:10.1002/pd.4945.
16. Lo KK, Karampetsou E, Boustred C, et al. Limited clinical utility of non-invasive prenatal testing for subchromosomal abnormalities. Am J Hum Genet. 2016 Jan 7;98(1):34–44. PubMed PMID: 26708752; PubMed Central PMCID: PMC4716686; eng.

•• **Study showing that the NIPT test sensitivity is a function of the fetal fraction, read depth and size of the fetal CNV.**