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LETTER TO THE EDITOR

Reply: The missing role of diagnosis of confined placental mosaicism in the management of fetal growth restriction

Dear Sir,

We thank Prof. Hantoushzadeh *et al.* (2021) for their interest in our review that evaluated the association between confined placental mosaicism (CPM) and pregnancy outcomes and fetal growth (Eggenhuizen *et al.*, 2021).

In our literature review, we have analyzed the impact of CPM on the fetal growth and found an increased risk of fetal growth restriction (FGR). In the reaction to our review, Prof. Sedigheh Hantoushzadeh and her colleagues advocated to perform a chorionic villus sampling (CVS) in case of FGR rather than performing an amniocentesis, in order not to miss placental chromosomal aberrations.

We acknowledge the importance of genetic testing in cases of FGR. In 2–19% of the FGR cases, a chromosomal abnormality is detected with karyotyping (Snijders *et al.*, 1993; Heydanus *et al.*, 1994; Bahado-Singh *et al.*, 1997). Diverse genetic problems can cause FGR and therefore, we advise single nucleotide polymorphism array testing in cases of FGR (de Wit *et al.*, 2017). Besides the fetal chromosomal abnormalities, we think CPM should be in the differential diagnosis. When the cause of FGR is found, the counseling of patients can be more precise.

To search for placental abnormalities, we suggest non-invasive prenatal testing (NIPT) additionally to an amniocentesis in case of FGR, instead of performing CVS. There is evidence that NIPT compared to CVS is more sensitive for the detection of CPM (Van Opstal *et al.*, 2020). The chromosomally abnormal cell lines can be restricted to small parts of the placenta, which can be missed by biopsy while performing CVS. Furthermore, the level of mosaicism found in the chorionic villus does not always reflect the level of mosaicism in the term placentae.

Unfortunately, based on the NIPT, a distinction between CPM types is not possible, because the NIPT only analyses the cytotrophoblast. We suspect that the type of CPM is a good indicator of the fetal outcome. More research is needed to confirm this hypothesis, such as the comparison of the ratio of the trisomic and fetal fractions. This can be of value to estimate the distribution of the chromosomal aberrations throughout the placenta. In case of high trisomic fraction as compared to a low fetal fraction, pregnancy outcome was favorable (Pertile *et al.* 2017; Brison *et al.*, 2018). This implies that trisomic fraction is a good indicator for aneuploidy-load in the placenta and thereby can help clinicians to predict pregnancy outcome and counsel patients more precisely.

In conclusion, we agree to advocate screening for placental abnormalities in case of FGR. Instead of using CVS, our favored method would be to perform an NIPT in combination with amniocentesis. Further research is needed to evaluate the role of NIPT as a diagnostic tool when a pregnancy is complicated with FGR. We hope to publish our retrospective cohort of CPM cases of the last 10 years, including the role of NIPT, in the near future.

Conflict of interest

The authors declare that there is no conflict of interest.

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Geerke M. Eggenhuizen[1,*], Attie Go[1], and Robert Jan Galjaard[2]

[1]*Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands*
[2]*Department of Clinical Genetics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands*

*Correspondence address. Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Center, 3015CN Rotterdam, The Netherlands. E-mail: g.eggenhuizen@erasmusmc.nl
https://orcid.org/0000-0002-0172-2529

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