Review of: "Non-Invasive Prenatal Testing (NIPT) for Aneuploidy in a Setting with a High Consanguineous Rate – A Retrospective Cohort Review of 1,153 Cases"

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Potential competing interests: No potential competing interests to declare.

Comments to author:

This is a good write manuscript, direct and simply, but there are 3 important things I am concerned:

First one, please show the mean and the interquartile range (Q1,Q3) of gestational week (GA) in Table 1. Based on figure 1, the gestational weeks are mostly 65-80 days, about 9-12 weeks. Fetal cfDNA fraction increase with gestational weeks, insufficient fetal cfDNA fraction is the most common cause for failure of NIPT. So in this study, lower fetal cfDNA fraction would be the most possible reason, which may cover the failure NIPT caused by consanguineous. As authors mentioned in Limitations and Strengths, it's a small sample size study, especially these cases' maternal age is a bit earlier, compared to other studies [PMID: 24657131; PMID: 36602559]. And we suggest authors read the below references and present a pointed discussion.

Yaron Y. The implications of non-invasive prenatal testing failures: a review of an under-discussed phenomenon. Prenat Diagn. 2016 May;36(5):391-6. doi: 10.1002/pd.4804. Epub 2016 Apr 2. PMID: 26941176.

Chan N, Smet ME, Sandow R, da Silva Costa F, McLennan A. Implications of failure to achieve a result from prenatal maternal serum cell-free DNA testing: a historical cohort study. BJOG. 2018 Jun;125(7):848-855. doi: 10.1111/1471-0528.15006. Epub 2017 Dec 6. PMID: 29090507.

Samura O, Okamoto A. Causes of aberrant non-invasive prenatal testing for aneuploidy: A systematic review. Taiwan J Obstet Gynecol. 2020 Jan;59(1):16-20. doi: 10.1016/j.tjog.2019.11.003. PMID: 32039788.

Second one, Yaron Y' review in 2016 concluded that the magnitude of NIPT test failures is associated with test methodology, especially for SNP -based approach. There were 6 commercial bands in this study, authors need introduce the methodology used by the 6 bands, MPS based or SNP-based. Consanguineous may don't increase the no result rate in MPS based method, but I think it may cause some affect on SNP-based NIPT. Because consanguineous is associated with higher level of homozygosity or fetal uniparental disomy (upd), which authors discuss it too. And in our study, fetal upd may cause NIPT positive result, but not no result (PMID: 36602559).

Third, I have a question, in Table 3, no result is 68 cases (25+41+2), while in Table 4, insufficient and not measure is 83

cases. So how many no result cases is actually in this study? And hope authors explain these no result cases possible reason in discussion part.

The other suggestions for improvement are:

Abstract

1 one of the brands (of the 4 most), I think it's a typo, would be 3, based the result rate 12.8% vs 3.9% and 3.2%.

2 There were 4 positive cases..., had they not requested testing. Sorry, I couldn't understand what they mean at here.

Subject and Methods

3) Pregnancy specific...CRL appear here firstly, please write out its full name.

4) mainly T13, T17, should be T18.

5) IRB approval for the study was exempt, please write out the full name of IRB.

6) family or family history, why repeat family here?

7) Please explain the high-risk test (>1:150), are you mentioning serum screening test or NIPT test? the high risk of NIPT usually use Z-score 3 as cutoff value.

Results

8) Table 2 title, better for "Indications for NIPT and related positive cases".

9) Figure 1 title, better for 'The change of cell free fetal DNA percentage with gestational age'.

10) The footnote of Table 3, the only reading, reading appears in the article two times , the other is below Table 3, 6 had low readings, I think it's meaning fetal fraction, better change it to fetal fraction or fetal cell free DNA percentage.

11) Table 4, miss number and a right bracket 20-4).

Discussion

13) In the second paragraph, 'In this series, there were...., rates were", what rates you mean here?

14) In the fourth paragraph, the 9th line, {m/44/}, please correct it. I think it's a reference.