Reviewer's report

Title: A New Fetal RHD Genotyping Test: Costs and benefits of mass testing to target antenatal anti-D prophylaxis in England and Wales.

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Reviewer: Anneke Brand

Reviewer's report:

General comment
The authors did a theoretical exercise to calculate costs and possible benefits from high throughput NIPD to detect a Rh-D pos fetus using 2 scenario’s. They conclude the predicted increase in sensitisations may be unacceptable high and reliability of the assay needs to be rigorously demonstrated. This conclusion is however not the purpose of their investigation and not based on their data but on other estimates from the literature, which may not be used entirely objective. In that respect I have the following questions and items that should be included in the discussion.

Specific comments

1
The fact that the current serological practice is not 100% reliable is not taken into account. Studies (also quoted by the authors) show that NIPD is more accurate than serology. Thus an estimate of cases prevented by NIPD as compared to current serology should be taken into account as well.

2
In table 3 the authors calculate scenario 1 based on a % of protection of antenatal prophylaxis presented by Mayne (BMJ1997). Have later reports not shown that the protection of antenatal prophylaxis is not that high? E.g.NICE 2008?

3
The advantage of NIPD not exposing the mothers unnecessarily to anti-D-Ig is too easily waved away. First it remains a blood product with minimal but not zero risks. Second, the authors argue that the anti-D supply in UK/Wales is not a problem as they purchase the product from the USA, unlike the Netherlands where they produce it from RBC-boosted donors. This is an important ethical aspect in avoiding unnecessary anti-D-Ig usage. In the Netherlands anti-D-Ig is derived from deliberately immunized donors. Do the authors know that USA donors are not boosted with red cells?

4
The authors should speak out why a particular scenario (e.g.1), assuming a
99.9% assurance that Rh-D + fetuses are not falsely typed as D-negative, even when it is cost-neutral is not advocated. Some studies claim a high correct prediction of D+s over 97%, which is likely higher than current practice. The arguments that they use now (robustness of the assay in Caucasian and ethnic minority populations needs to be demonstrated), does not need a cost calculation, because in case of an inferior technique even major savings would not lead to advocating NIPD.

Minor comments
Is the Rh-D sensitivity of NIPD only based on false-negatives? Please indicate that more clearly in legends table 3.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
'I declare that I have no competing interests'