Author’s response to reviews

Title: OBSTETRICAL PROVIDER KNOWLEDGE AND ATTITUDES TOWARDS CELL-FREE DNA SCREENING: RESULTS OF A CROSS-SECTIONAL NATIONAL SURVEY.

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Reviewer 1

This is a timely study that appropriately examines Canadian obstetric provider knowledge of and opinions about cfDNA screening. I agree that the findings are relevant and of use to stakeholders in the field of prenatal care. A few areas that I think could be improved:

1. It would be useful to international audiences to provide more up front background on the Canadian health system and how OB care is generally delivered. The fact that cfDNA is not included in the standard of care (ie it must be purchased from a commercial provider out of pocket) is a useful frame for the survey itself as this may be relevant to why providers were more or less aware of the screen and its capabilities.

   Thank you for this observation. We agree that setting a background for international readers regarding the structure and delivery of Obstetrical care in Canada is essential for putting these results into a larger context. The Introduction section now been elaborated to include this feedback. Line 91

2. Additional information on how the survey was developed would be appropriate. The authors do not discuss which aspects of cfDNA they decided to address and why. Presumably they used some of their own knowledge to assess which elements of cfDNA knowledge were most clinically relevant but this needs more explanation.

   Further information elaborating on the process used to construct our survey has been added to our Methods section. Furthermore the full survey in English and French has been included as an Additional File for further transparency.
3. The authors seem to avoid making affirmative statements about the implications of their results. In the Discussion, they state that the study was not intended as a needs assessment but if this is true, it is not clear what the purpose of the study was. Why assess provider knowledge if you are not going to assert that a) provider knowledge is essential to the ethical and clinically responsible use of cfDNA and b) if there are gaps in knowledge, concrete action is needed to fill them. For instance, the fact that half of the providers surveyed didn't know that maternal weight impacts the efficacy of cfDNA is alarming. While I understand the authors' reluctance to 'call out' their colleagues, a clear call to action would be appropriate.

Thank you for sharing your thoughts regarding our assertiveness regarding the implications of our study. We do agree that this study is indeed a needs assessment tool and we have revised our discussion to remove the phrase: “Although our study was not performed primarily as a needs assessment tool” previously line 249. However, it is our belief that our conclusion statements are in fact definitive in stating that there are significant gaps in knowledge, which must be corrected. In fact, we close our manuscript with “As we go forward, it is important we evaluate knowledge gaps and provide learning tools to all obstetrical providers so that we can embrace the benefits of this novel and promising technology while protecting the integrity of the informed consent process.”

Reviewer 2

1. Please provide a reference to support the notion that smoking is associated with cfDNA screening test failures. Publications such as Ashoor et al., Fetal Diagn Ther, 2012, and others, clearly show no association of fetal fraction and maternal smoking which would suggest no impact on test success., Line 184 (errata quiz, explain why)

Thank you for pointing this erratum out. This was an unfortunate mistake incorporated into our survey and propagated into our original discussion. The question was initially explored by determining factors which can affect fetal fraction (positively or negatively) and unfortunately it was overlooked and erroneously grouped with other factors that are associated with low fetal fraction (BMI, CRL, etc…) As you have astutely pointed out, smoking is not associated with low fetal fraction and thus test failures. In fact a study by Ashoor et al. in 2013 found the median fetal fraction was increased by 7.5% in smokers and other subsequent studies have found no differences between smokers and non-smokers. This has been pointed out as one of our limitations in our Discussion section (line 309) and the association between smoking and fetal fraction clarified.

2. Most professional societies in the USA (ACOG (# 163, May 2016), ACMG, etc.) are permissive with regard to cfDNA screening for ALL pregnant women. Furthermore, they have provided extensive guidance on education. Please address these documents in the Introduction.
Thank you for this feedback. Indeed, Canadian and American professional societies do differ in their recommendations regarding offering cfDNA to ALL women. The major difference in opinion being due to the fact that cfDNA screening has yet to be deemed cost-effective as a form of primary screening in all women across all Canadian provinces. We have revised our introduction to elucidate these differences. (Line 79)

3. Contrary to the statement in the Discussion, page 12, line 245, there are other USA based publications on physician knowledge about cfDNA screening and these should be included in the manuscript (Palomaki et al, Genetics in Medicine, 2017; Gammon et al., Ethics Med Public Health. 2016.)

Yes, more recent publications such as the ones mentioned above have been published since our original submission to BMC. Our manuscript has been updated to include these publications and other. Please see line 266.

4. The practice of termination for screen positive cfDNA results without diagnostic confirmation is concerning and should be discussed further. Dobson and colleagues speak to this issue in a new publication (Prenatal Diagnosis, 2016).

Indeed this is a concerning issue, thank you for recommending this recent study by Dobson et al. This issue is discussed further. Line 268

5. Page 4, line 56. For 95% detection, the false positive rate is 23% for first trimester combined test and 5% for the full integrated test. The false positive rate should be quoted as 5-23%.

Indeed you are correct, this oversight has been corrected.

6. Page 4, line 64. Omit %

Corrected, thank you for pointing this out.

Editor Comments

Thank you for your submission to BMC Pregnancy and Childbirth. In addition to addressing the reviewers' comments, please address the following editorial points:

1. Please include email addresses of all authors on the title page.

The title page has been updated to include email addresses for all authors.
2. Please include a "Consent to publish" statement in your declarations. If this does not apply to your study type, please put "not applicable."

Thank you for pointing out this oversight, statement added.

3. Please remove all color and shading from your tables.

All colour and shading have been removed from tables as per publishing guidelines.

4. You mention that the English version of the survey is in Appendix A, but no such file was included. Please include the survey in both English and French as Additional files and include a section at the end of your manuscript listing all Additional files.

Both French and English versions of the survey have been added as Additional Files at the end of the manuscript.