Author's response to reviews

Title: Effect of Iron Content on the Tolerability of Prenatal Multivitamins in Pregnancy

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Author's response to reviews: see over
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To the BioMed Central Editorial Team,

Thank you for reviewing our manuscript entitled, “Effect of Iron Content on the Tolerability of Prenatal Multivitamins in Pregnancy”.

In general, we have found the reviewers’ comments most useful and have addressed them fully. The following is a point-by-point response to the comments, noting any changes that were made to the manuscript or addressing any questions or concerns raised:

Reviewer: Anne-Louise Heath

Major Compulsory Revisions

1. The study design is not able to provide data in support of the author conclusions that iron content (35 mg vs 60 mg elemental iron) is not a major determinant of compliance with prenatal multivitamins, and tablet size appears to be the more definitive factor affecting compliance because the tablets in the current study differ in a number of ways that may influence compliance independent of iron content. Specifically, the 35 mg iron tablet, compared to the 65 mg iron tablet: (a) has a larger volume, (b) is a different shape, (c) is given in 2 doses per day rather than one, and (d) contains a different iron compounds (fumarate vs sulphate). The authors must therefore limit their discussion and conclusions to statements that can be supported by their study design. These will be need to be about the 2 specific products tested and are therefore not of wide scientific interest.

Response 1:

Our primary focus of the current study was to determine if the lower iron content would improve the tolerability of prenatal multivitamins in pregnancy, while factoring in tablet size was secondary. Although the volume and shape of the 2 multivitamins differ, both are ‘small size’ tablets compared to standard prenatal multivitamins which are usually horse pill size and shape. In our previously published study, which was cited in the Background (page 3, paragraph 3, line 1), we compared the 35 mg iron multivitamin (PregVit®) to a standard prenatal multivitamin (Materna®) and this pilot study suggested that there was improved tolerability with the 35 mg iron tablet. However, it was of interest to isolate the potential effect of iron content, thus we conducted this current study comparing 2 small-size multivitamins, differing in iron content, as was noted in the Background (page 3, paragraph 3, line 3).

In our revised Discussion section, we address the comments about different iron compounds (fumarate vs sulphate) (pg 12, paragraph 2, line 2) and the twice-daily dosing vs. once-daily dosing (pg 12, paragraph 2, line 4). Based on available knowledge to date, it did not contribute to a significant difference in rates of adherence or reported GI events.

2. Include in the Discussion comments on the specific nature of the population studied, that is pregnant women (a) who had contacted the Motherisk program presumably with concerns about maternal exposure to drugs, chemicals, and disease, and (b) 66% of whom had a history of
discontinuing multivitamin supplement use in the current pregnancy; and the extent to which these findings can be applied pregnant women in general.

Response 2: The specific nature of the population studied is addressed in the Discussion (pg 11, paragraph 1, line 1), with an explanation of how the findings may be applied to the general population of pregnant women.

3. Please remove the statement in the Introduction that: no study is presently available which has separated the effect of iron content, as opposed to the tablet size, on tolerability because this implies that this question has been answered in the current study.

Response 3: We have removed the statement.

4. There needs to be more discussion of the methodology used to collect the adherence data and how this may have impacted on the findings. In particular, do you have data that suggest that a monthly recall of pill intake provides valid estimates of actual pill intake in the previous month?

Response 4: Thank you, we have addressed the issue of pill intake recall in the Discussion (pg 11, paragraph 4, line 1), with reference to other studies employing pill intake recall.

5. Please state in the Methods how discontinuation of the tablet regimen was defined – was the date of discontinuation the date reported by the mother in a recall interview, or was it the date of the first recall interview at which the discontinuation was reported? How might this have impacted on the results?

Response 5: We have defined ‘discontinuation’ in the Methods section (pg 7, paragraph 1). Since we relied on the subject reporting the date of treatment discontinuation, the impact of self-report is similar to that of pill intake recall which had already been addressed in Response 4.

6. Please state in the Methods how the number of pills prescribed was determined – from participant recall? From information collected directly from the prescribing health professional?

Response 6: We have defined in the Methods section (pg 7, paragraph 2, line 7) how the number of pills prescribed was determined.

7. I would advise statistical advice to determine whether there are more powerful statistical methods that may be more appropriate – i.e. using the adherence data as a continuous variable, controlling for gestational age, etc.

Response 7: Our statistical analysis was supervised by a professor of biostatistics, Dr. Amalia Levy. Dr. Levy, a co-author, is of the view that our statistical analysis involving chi-squared tests and Kaplan-Meier survival curve analysis were appropriate to compare the adherence rates between treatment groups in a cross-sectional (i.e. proportions starting or not starting assigned multivitamin) and longitudinal (i.e. proportions continuing to take assigned multivitamin over time) manner.
Minor essential revisions

8. The description 35 mg ferrous fumarate and 60 mg ferrous sulphate should be corrected to 35 mg elemental iron as ferrous fumarate.

Response 8: The description has been corrected in the Methods section, under the sub-section of “Selection of prenatal multivitamin for study comparison” (pg 5, paragraph 2, line 1; pg 6, paragraph 1, line 2).

9. Need to reference statements in Introduction about tablet size aggravating GI symptoms and multivitamins worsening GI conditions.

Response 9: The sentence about tablet size has been re-phrased to state that GI symptoms may be “…aggravated by the iron content and swallowing a large tablet” (pg 3, paragraph 2, line 3) which clarifies that the GI irritability may result from swallowing difficulties or aversions to swallowing large size items. As suggested, references have been added.

Secondly, the sentence about GI conditions has been re-phrased to “…some women may experience exacerbation of GI conditions such as…” (pg 3, paragraph 2, line 8) which notes the GI sensitivity of women with GI conditions – but it no longer states that multivitamins aggravate GI conditions.

10. Differentiate between Tables 2a and 2b by incorporating the content of the first footnote in the title. Similar for Tables 3a and 3b.

Response 10: Based on the suggestion by another reviewer, Table 2b and 3b have been omitted. The titles of Tables 2 and 3 incorporated the footnote content into the titles.

11. The key to Figure 2 is not clear, please re-label.

Response 11: The key has been re-labeled in Figure 2.

12. Please make the format of Figs 2 and 3 consistent – including use of the same coloured line for the 2 groups in both Figures.

Response 12: The format of Figures 2 and 3 have been revised to be consistent.

Discretionary Revisions

13. Have the authors considered using the term adherence rather than compliance to describe the relationship between their participants and the intervention.

Response 13: As suggested, the term compliance and compliant has been replaced with adherence and adherent, respectively.
Reviewer: Nils Milman

14. Introduction: Previous studies on this subject should briefly be mentioned.

Response 14: As suggested, previous studies are cited in the Discussion as it was the appropriate section to note that our findings were consistent with the findings of these previous studies.

15. The introduction should be shortened and focus on the aim of the study.

Response 15: As suggested, the Background was shortened. We felt the Background must provide a clear description of how multivitamin supplementation is challenging in pregnancy, to lead to the current study which aims to examine if a change in the iron content of the multivitamin can reduce GI irritability.

16. Results: Table 2b and 3b can be omitted. There should only be one Figure, I suggest Figure 1 is omitted. It should be clear from the text in Table 4 that the recorded data are obtained during supplementation.

Response 16: As suggested, Table 2b and 3b have been omitted. We would like to retain Figure 1. Figure 1 is a common flow chart describing enrolled subjects and is important in outlining the randomization and the drop-outs. If we omitted Figure 1, we would have to include the information as descriptive text in the Results section which then lengthens the text in the Results section and it may not come across clearly as it would in a flow chart manner. Figure 2 and 3 depict the Kaplan-Meier survival curve analysis of adherence data and is vital to demonstrating that no significant difference was detected between treatment groups over time, despite the 35 mg iron multivitamin being taken twice daily. The title of Table 4 clearly stated that the data was obtained “among pregnant women who started taking the assigned multivitamin”.

17. Discussion: Should be more concise and compare with the results of: Kerr and Davidson paper and Milman et al. paper.

Response 17: Our Discussion has been revised to be more concise, specifically addressing the results (adherence and adverse events rates) and factors such as the study population, the randomization, and the presence of nausea and vomiting of pregnancy which may affect the results. Reported adverse GI events were compared to the results in previous studies (see Discussion, page 12, paragraph 2, line 3) and previous studies, as suggested, were cited in the Discussion.

18. The low compliance and consequently small series of women in the 2 groups is a considerable disadvantage to the study.

Response 18: We believe that the low adherence is a key finding as it shows that even with follow-ups and reminders, women do not comply. This must mean that in “real life”, adherence is even lower. This has been added to the Discussion. The issue of sample size is addressed in the Discussion (pg 11, paragraph 2).
Reviewer: Leslie W Huson

Major Compulsory Revisions

19. 92 vs 74 randomized to the 2 arms – this inequality seems a little unusual in a study being randomized at a single source. The authors should confirm in the MS that this difference was not due to any differential drop-out or refusal to take randomized medication i.e. that this difference is entirely due to different numbers being randomized into the 2 groups.

Response 19: The issue of unequal randomization is addressed in the Discussion (pg 11, paragraph 2), specifically noting that there was no difference in the drop-out rate between treatment groups.

20. Table 1: This table should split all data between the 2 treatment groups the purpose is surely to try to demonstrate that there are no important differences between the 2 groups at baseline.

Response 20: As suggested, Table 1 has been revised to split the data between the 2 treatment groups.

21. Table 2a/b – the conventional approach to analysis of randomized studies is to report data based on the Intent-to-Treat (ITT) paradigm. This table reports data for Completers only (Completers with some data) and hence is possibly biased.

This table should as a minimum report for the ITT population, with an assumption that patients who did not complete were not compliant. If the authors also wish to present data for the other groups, they could do so but only after showing the ITT results.

Response 21: It should be clarified that partial data from subjects who did not complete the study were included in the analysis as was shown in Tables 2b and 3b; however based on the suggestion of another reviewer, Tables 2b and 3b have been omitted and it was stated in the footnote of Tables 2 (previously 2a) and 3 (previously 3a) that the partial data did not contribute a significant difference to the analysis, thus did not change the results.

The ITT paradigm was difficult to apply to the current data analysis because the assumption that “patients who did not complete [the study] were not compliant” is an inappropriate assumption for this study of pregnant women. As shown in Figure 1, some subjects did not complete the study because they, for example, miscarried or terminated the pregnancy and thus may not have had a chance to even start the assigned multivitamin since the reason for taking a prenatal multivitamin (i.e. being pregnant) no longer existed. We lost contact with some women shortly after they were enrolled in the study and thus, never had a chance to inquire about them starting the assigned multivitamins. Here too, it is inappropriate to assume they were not compliant because we really do not know.

22. Table 3a/b – the same comment applies – show ITT data as a minimum.

23. Figures 2 and 3 are badly presented. They show “time-to-event” curves for the same groups of patients, but the labeling style differs between the tables, the colour of the plots differs, the unit of time on the x-axis, etc. These 2 figures should be re-done with more consistency.

Response 23: As suggested, Figures 2 and 3 have been revised to be more consistent.

24. Table 4 – it seems likely that this table is biased as an indicator of adverse event rates in relation to iron content, as it presents data only for patients who complete the study. Completers, almost by definition, probably have a lower probability of experiencing an adverse event. For this reason, I think that the authors should omit the statistical significance tests from this table and present the data as descriptive only. They should also present the percentages based on the ITT population as well as the completer population.

Response 24: It is important to note our definition of ‘study completion’ as stated in the Method section (pg 7, paragraph 2, line 1). Study completion was based on subjects completing the monthly telephone interviews up until the end of pregnancy, whether or not they started the assigned multivitamin. Therefore, a ‘completer’ is not by definition someone who probably had a lower probability of experiencing an adverse event. Hence, we do not believe this introduces a bias.

Furthermore, the title of Table 4 clearly states that the data of reported adverse events was “…among pregnant women who started taking the assigned multivitamin”. If a subject did not start the assigned multivitamin at all, she is not likely to have any adverse events to report or if she does, it cannot be due to the assigned multivitamin since she did not start taking it.

The statistical significance tests were removed to keep Table 4 more as a descriptive table.

Formatting Changes
The following sections, with the correct information, have been incorporated into the manuscript as instructed: a) competing interests, b) authors’ contributions, and c) acknowledgements have been included in this order after the concluding statements and before the Reference list.

We appreciate the comments regarding our manuscript and have addressed the issues raised to the best of our knowledge. Each authors has participated sufficiently to qualify as an author and they have all seen and approved the manuscript. Thank you for your help in improving the quality of our presentation.

Sincerely,

Gideon Koren