

## Author's response to reviews

**Title:** A randomized cross over trial of tolerability and compliance of a micronutrient supplement with low iron separated from calcium vs high iron combined with calcium in pregnant women [ISRCTN56071145]

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### Author's response to reviews:

Thank you for your letter of December 24, 2005, and for the attached reviewers' comments. In general we have found those comments most useful in revising our manuscript as follows:

Dr. Czeizel:

\* As suggested, we have changed the term "multivitamins" to "micronutrients" throughout the manuscript.

\* We agree that the issue of educating parents to be on the importance of folic acid is paramount. We have added this point to the Discussion.

\* The rates of diarrhea were minimal and not different between the arms. This has been added to the revised manuscript.

\* Thank you for the note about rates of prevention of other malformations. We have added Botto's reference and have changed the percentage figure.

\* Nausea and Vomiting of Pregnancy WAS quantified by a validated tool (Table 2), which is more accurate than categorical "mild", "moderate", "severe". There is wide criticism against the use of "mild" and "moderate" NVP as these are subjective. Moreover, the severity of NVP based on the validated score was entered as a variable in the multivariate analysis. These details have been added to the manuscript.

Dr. Merchant:

Dr. Merchant states that "it seems that NVP was the main outcome of interest because the block randomization ..... was done whether or not it was present". Block randomization by specific factors is done when the particular factor (e.g., NVP) may affect the primary outcome (in our case adverse events). Our a-priori main outcome of interest was adverse events including compliance rate. Because NVP may change along pregnancy, it was critical to randomize women to receive first Pregvit/Materna so there is equal chance of actual improvement. We believe that throughout the analysis, results and discussion it is clear

that the primary endpoint is rates of adverse events and that NVP (yes/no) and its severity score (from 3 to 15) are potential confounders. To ensure clarity, we have added a statement to the "Sample Size and Statistical Analysis Section".

As suggested, the mean gestational age has been added. Women starting on either arm of the study were of similar gestational age. These details have been added to the manuscript.

Dr. Merchant claims that the "loss to follow-up was too large to be able to draw any valid conclusions. If the participants were dropping out because of one or other medication, the persons remaining in the study may have compliant rates that would be different from those who dropped out".

We have discussed the drop out rate in the original manuscript, and have added points to address the reviewer's comments':

\* The drop out rate was equal between the two arms, so there was no bias based on the intervention arm (Pregvit vs Materna).

\* Most women withdrew because of lack of motivation of healthy pregnant women to participate in this intense protocol, including daily diaries and returning pills. However, because each woman served as her own control in this cross over design the attrition does not bias the results in favor of one arm on the other.

\* Because compliance rate was an important end point, it was critical for us to conduct the study as naturalistic as possible, hence refraining from contacting the women to remind them of their participation.

We have made these points more clearly in the discussion.

We wish to thank the reviewers for their help in improving the quality of our presentation.

Sincerely,

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