Author's response to reviews

Title: Essential fatty acids for premenstrual syndrome and their effect on prolactin and total cholesterol levels: a randomized, double blind, placebo-controlled study

Authors:

Edilberto A Rocha Filho (edilbertorocha@globo.com)
Jose C Lima (rlos UFPE@yahoo.com.br)
Joao S Pinho Neto (sabinopinho@terra.com.br)
Ulisses Montarroyos (ulisses@cpqam.fiocruz.br)

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Author's response to reviews: see over
Dear Editor of Reproductive Health

Ref.: Manuscript MS: 1715217629440308, Essential fatty acids for premenstrual syndrome and their effect on prolactin and total cholesterol levels: a randomized, double blind, placebo-controlled study

Dear Sir

First of all I would like to thank you and the reviewers for the careful revision of our paper, giving important suggestions for improving its quality. The changes in the text are marked with fast track. The answers for the specific questions of the reviewers are below in bold:

Reviewer’s report 1: This is a well done and well written small randomized placebo controlled trial on the treatment of premenstrual syndrome with two different doses of essential fatty acids. The outcomes of the study are the effectiveness and safety of these drugs in reducing the median scores of symptoms associated with the syndrome, using a standard and validated scale specifically designed for that. This is important due to the high frequency of this condition and the relatively few evidences available on effective treatment.

Major Compulsory Revisions:

There is no explanation on the sample size estimate. Please provide it or explain why it was not presented. OK, this was included in the methods session.

Minor Essential Revisions:

The first part of the discussion has no references for some statements. Please check the text and include some. OK, included.

Discretionary Revisions

Level of interest An article of outstanding merit and interest in its field

Quality of written English Acceptable

Statistical review No, the manuscript does not need to be seen by a statistician.

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

Reviewer’s report 2: Major compulsory revisions:

The authors reports the outcomes of a study aiming to show the effects of essential fatty acids (EFA) administration on the symptoms of premenstrual syndrome (PMS) and circulating levels of total cholesterol and prolactin (PRL). In the manuscript, the scientific background should be addressed much more straightforwardly and the rationale of the study should be defined more precisely, as this topic is widely debated and very poorly understood among clinicians. In example, the effects of EFA on prostaglandins and the relevance of prostaglandin changes in PMS should be highlighted and explained better according to the literature, as this pathway
appears to be the most likely effector of the putative EFA effects on PMS. In addition to this issue, an improved characterization of the link between prostaglandins and PRL is required. Finally, the possible relevance of changes of PRL levels or peripheral sensitivity to PRL should be more exhaustively characterized.

**OK, these aspects are considered in a new paragraph included in the introduction.**

The hormonal parameters (including gonadotropins and sexual hormones) and the full lipid profile of the patients should have been checked in a homogeneous and exhaustive manner and be reported. This will help to clarify that no subclinical endocrine or metabolic abnormalities affect the patients studied and, consequently, the study outcomes. A patient with hyperprolactinemia was excluded from the data analysis. Was she excluded following an inappropriate inclusion or due to the development of hyperprolactinemia later on? If hyperprolactinemia occurred later (as reported by the authors in the Discussion), which was the cause of that and why the patient has been excluded from the data analyses? This point should be clarified and, eventually, discussed.

**OK, these points were clarified in the text.**

The opportunity to enroll patients approaching the menopause should be reconsidered, as they can develop physiological changes of their symptoms over the study. Considering that the authors wanted to study the effects of EFA on cholesterol, I think that the study needed to be addressed also to HDL, LDL, and triglycerides, at least. Lack of these parameters makes the study significantly poor for the goal.

**OK. The effect of studying women approaching the menopause we think is controlled by the fact that the three groups are similar. In addition, it is worth to remember that the total duration of study follow up was of only six month (a relatively short time to observe time trends in symptoms) and that the mean age of women in the three groups were around 32/33 years (no significant difference and relatively far from the mean age of menopause). Unfortunately, other laboratory parameters like HDL, LDL and triglycerides were not considered during study implementation and therefore can not be reported at all now.**

The PRISM calendar should be characterized more precisely. It is a 23 (not 26 or 36, as reported in the manuscript) symptom issues questionnaire with additional 11 lifestyle evaluation points, 4 life event reports, and infos about body weight changes and concomitant medications. The symptom scale range from 0 to 3, while the other questions need a yes/no answer only.

**OK, this was clarified accordingly.**

Although the authors did not demonstrate any faster effect of the EFA highest dose than the lowest one, they report many times that the effects of the 2 grams dose was faster. Actually, they did not study the timing by which the medication was starting to exert its effects. I guess that they have erroneously confused the term and thay were meaning something like "bigger", "more evident", or "more pronounced" instead of "faster" and "more rapid".

**OK, these terms and words are changed accordingly.**
I do not think that this study is strong enough to show that EFA represent an "important therapeutic option for patients with PMS". On the contrary, this study appears to confirm what already known from the literature (in some patient series, at least) about the possible beneficial effect of EFA for controlling some psychological or emotional aspects of PMS. However, my understanding is that there is no general agreement about the EFA beneficial effects in PMS patients among the clinicians. Definitely, no "new evidence in support of the use of EFA in PMS patients" have been clearly demonstrated by the authors, on the contrary of the statement in the 2nd paragraph of the Conclusions.

**OK, these considerations were put in a more general way, without highlightening any strong effect.**

In my opinion, the authors conclusions about the effects of EFA administration on PRL receptors through PGE1 are not based on any of the issues analyzed in the study and may just represent an hypothesis. Also the sentence about the lack of detrimental effects of EFA on lipid metabolism is excessively conclusive as the authors did report on total cholesterol only. I find Table 2 as poorly readable. In Table 3, it is unclear to me the meaning of the statistical comparisons done and actually I do not get any comparison among the three groups. I think that review of the statistics by a statistician is required. Are the tests used for the statistics suitable and appropriate for the scope indeed?

**The statements in the conclusions were reworded following these suggestions. For table 2 the title of the last column was changed because in fact it reflects the comparison of the difference score among the groups. The data was again reviewed by a statistician.**

The manuscript is very poorly written both from a language and a scientific style point of view. I think that it should be re-written and made much more accurate in describing the background, the methods, and the results. The Discussion should focus on the meaning of the results reported and discuss them in the context of the literature, avoiding redundant comments and sentences. Finally, the Conclusions should be re-written in a smoother way and should be based solely on the results concretely observed in this study. The manuscript structure needs a much better organization and both data and comments requires a much more organized outline. Also the abstract should be carefully re-written according to the manuscript changes and follow a precise and exhaustive outline (in example, the Background section does not provide any background at all).

**The manuscript was extensively reviewed and redundant comments were withdrawn.**

In the Competing Interests section, the authors have not clearly stated their competing interests, if any, or the absence of them.

**OK, included.**

Minor essential revisions:

Some references about data from literature are missing. At the end of the 4th paragraph of the Background, the term "victims" should be changed to "patients" or "subjects". Reference 21
appears to me to come up in the text before Reference 20. Some sentences and a few paragraphs over the manuscript appear to be redundant. Figure 1 and Legend to Figure 1 should appear sequentially for clarity reasons.

**OK, changed.**

Discretionary revisions:

Do the author consider the possibility to assay prostaglandins levels in the patient groups to try and corroborate their hypothesis?

**Yes, we thought. But the prostaglandin serum levels are very difficult to be determined and also very expensive and we had no way to perform it.**

**Level of interest** An article of limited interest