Reviewer's report

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

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Reviewer: Gianluca Tamagno

Reviewer's report:

Major compulsory revisions:

The authors report 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.

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.

The opportunity to enrol 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.

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.

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 they were meaning something like "bigger", "more evident", or "more pronounced" instead of "faster" and "more rapid".

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.

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 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).

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

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.

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

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

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.