Author’s response to reviews

Title: Pravastatin induces NO synthesis by enhancing microsomal arginine uptake in healthy and preeclamptic placentas

Authors:
Zita Páncél (drpanczelzita@gmail.com)
Zoltán Kukor (kukor.zoltan@med.semmelweis-univ.hu)
Dorina Supák (supakdorina@gmail.com)
Bence Kovács (kovacsgezabenedek@gmail.com)
András Kecskeméti (kecso@vipmail.hu)
Rita Czizel (czizel.rita@gmail.com)
Magdolna Djurec (magdi.dj@gmail.com)
Bálint Alasztics (dr.alasztics@gmail.com)
Krisztián Csomó (foncsorozas@gmail.com)
András Hrabák (hrabak.andras@med.semmelweis-univ.hu)
Sándor Valent (valent.sandor@gmail.com)

Version: 1 Date: 09 Jul 2019

Author’s response to reviews:

Dear Editor,

Thank You for reviewing our manuscript (Manuscript No. PRCH-D-19-00653), entitled "Pravastatin induces NO synthesis by enhancing microsomal arginine uptake in healthy and preeclamptic placentas". We have carefully studied and appreciated the criticism and comments of the Editor and Referees. The paper was rewritten to answer raised questions and criticisms. Specifically, additional data were included (highlighted with yellow).

We hope that with these changes, the paper can now be found acceptable for publication in BMC Pregnancy and Childbirth and matches the high standards of Your journal.
We are grateful for the careful reviewing of our manuscript. We have thoroughly studied the Reviewers precious comments and our responses are as follows:

Answers for the comments of Reviewer 1:

1)

Abstract
You start you abstract with "Impact of Pravastatin". When you say impact, you need to explain impact in what. I understand what you mean; however the way it is written is not clear.

-Corrected pp. 2

You also need to explain what "NO" means for the reader.
-NO was explained, nitric oxide was written. pp. 2

The methods section is incomplete. You need to explain what type of study, population, period of data collection and statistical analyses.
At the results you included the co-treatment with Geldanamycin. This should be before in methods.
-Corrected pp. 2

Key words: I suggest including Placenta.
-Placenta was entered. pp. 3

Background.
You start saying that preeclampsia is the leading cause of maternal mortality. However hemorrhage is the leading cause in the world. If you have another data, you should include where preeclampsia is the leading cause of maternal mortality.
-Corrected pp. 4

Again you need to explain what NO is at the text.
-NO was explained, nitric oxide was written. pp. 4

Paragraph 3. I suggest including a graph with all these mechanism for better understanding since is the main explanation for your manuscript.
-Figure 1. (new figure) includes these mechanism.

Overall all the information at background is good. However, is disconnected and confusing. I suggest rephrase the background linking the paragraphs and the information. I also suggest including the safety of using statins during pregnancy.
Methods
There is some repeated information. You should explain how was the selection of the placentas, if it was sequential cases, the worst ones, or randomly. Otherwise, you need to include how the clinical information was collected. Interviews? Medical records? Women signed the informed consent? Agreed to participate at the study?
-Corrected. The missing informations are inserted. pp. 4-5

What is not clear for me is when did you include Pravastatin? The pregnant women with preeclampsia took them or did you include at your experimental phase? I know that you used during the experiments, however must be very well explained at methods.
-Corrected pp. 5

Results:
Again, there is some information repeated.
The definition of preeclampsia should be at methods.
-Corrected

The figures should include footnotes with the explanation of the * symbols. It is still not clear. The figure 1A is the control - ok. And the figure 1B you compare with the inclusion of Pravastatin? Am I right? So, the legend for figures 1A and 1B are confusing. Also, the results should no be at the legend but described in results. Also, you need to introduce the figures before show the results: Figure 1A shows… and we found….
-Corrected

Discussion
I suggest that the discussion could be written with the following information: Summarize primary findings of your study/ Discuss two to three interesting findings/ Strengths/limitations/ Next steps/ Conclusions. I also suggest you to discuss how the differences in gestational age could (or not) have influenced the results.
-Corrected pp. 6-7

Answers for the comments of Reviewer 2:

1)

BACKGROUND
p4 line 4: Preeclampsia is a leading cause of maternal mortality, not the leading cause (that is postpartum haemorrhage)
-Corrected

p4 line 40: The authors could more clearly describe the pilot study they are referring to - patients at high risk for pre-eclampsia? It is unclear.
-Corrected („with a history of severe preeclampsia in a prior pregnancy” was written)

p4 line 43: A definition or explanation of placental microsomes would be useful. They are discussed throughout but not once explained.
-Corrected
METHODS
p4 line 56-60: repetition of methods previously described in section 1.
-Corrected (data are in section 1.)

RESULTS
In general, I think the results should be presented in a table as well as graphically so the reader can clearly see means, p-values and SDs in one place. This may be personal preference but I feel it would make the data easier to interpret.
-Corrected (data are in Figures).

I found it quite hard to follow the results, this may be my inexperience of the type of experiment conducted but I do think the authors could more clearly describe their findings. Perhaps a more detailed description of results in the text would help.
-Where necessary, corrected

p6 line 2-5: Clinical definitions and inclusion criteria should be moved to the methods section
-Corrected (data are in Methods). pp. 4-5

p6 line 21-24: It is unclear what data are being described here - Figure 2?
-Corrected (text includes Figure 2)

p6 line 28-33: I think this section is supposed to reference figures 3A and 3B rather than 2A and 2B. Apologies if I missed something.
-Corrected

p6 line 40: I think this is meant to be Figure 4, not 3.
-Corrected. Sorry for the mistakes

DISCUSSION:
I think this section would benefit from discussion this study's findings first, then those of others reported in the literature.
-Corrected

I feel the results are overstated. No study limitations are discussed. Potential selection bias, small sample size, measurement error?
-Corrected pp. 8

p7 line 33-36: The authors should not make recommendations for clinical practice, their study is a small ex-vivo experiment.
-Removed

p7 line 46: It is unclear what the authors mean when they say 'our results of arginine uptake account for previous observations on the effect of statins'. Please expand on this point or clarify. Apologies for my misunderstanding.
-Corrected

TABLE AND FIGURES
Table 1 has no title and blood pressure has no units.
-Corrected (mm Hg)

The figures and table lack a key. It is unclear what the symbols and abbreviations represent. The figure descriptions contain text describing the results which is repeated in the main results section. I don't think it is needed here. These are repeated in the figure descriptions too. It would be better to describe the figure itself rather than the results.
-Corrected