Prof Jin-Xin Kong

Scientific Editor, World Journal of Obstetrics and Gynecology

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Dear Prof Jin-Xin Kong,

Please find enclosed a modified version of our manuscript entitled “miRNAs: new players in endometriosis”, for publication in *World Journal of Obstetrics and Gynecology*. We would like to thank you and the referees for your comments, since it has made it possible to significantly improve the manuscript. We have incorporated your suggestions as you can find answered one by one using the required format.

We hope these changes adequately address the questions raised by the referees and will permit the manuscript to be publishes in *World Journal of Obstetrics and Gynecology*. Thank you very much again to accept the manuscript with minor modifications.

All the authors have read and approved submission of the manuscript, and confirm that the manuscript has not been published and that it is not being considered for publication elsewhere, in whole or in part and in any language except.

There are no commercial associations such as consultancies, stock ownership or other equity interests or patent-licensing arrangements that might pose a conflict of interest in connection with this article.

Looking forward to hearing from you soon,

Yours sincerely,

Juan Gilabert Estellés, MD, PhD

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Author contributions: Name and family name of all authors have been changed to the right format.

Title on full name of institution of corresponding author: This point has been addressed according to suggestions.

Telephone and fax format have been changed according to suggestions.

Answers to comments by *reviewer 00742253*:

I would like to congratulate the Authors on a very good paper. This is an interesting review and could be of interest for the readers. Because this is a review, I suggest to asses the methodological quality of published papers.

Thank you very much for your comment, which we do appreciate.

Answers to comments by *reviewer 03270459*:

I do appreciate the authors' effort on this paper entitled "microRNAs: new players in endometriosis". This is an interesting review exploring the exact role of miRNAs in the pathophisiology of endometriosis on the basis of the interpretation of previous similar articles. Language was good and concise. I recommended a publication of this paper in the magazine only after the complement of some information.

1、 Better to add more information on the role of miRNAs in the pathogenesis of endometriosis.

Recent literature on the issue has been discussed throughout the review.

2、 Citations of recent and relevant literature on various types of miRNA, such as miR-30c, miR-200c in endometrial carcinoma are needed.

In this review we were intended to give a panoramic view of the current status of the art regarding the involvement of miRNAs in endometriosis, in terms of physiopathological mechanisms and diagnosis. However, updated literature regarding the aforementioned miRNAs in several gynaecological malignancies has been discussed in lines 123 to 137.

3、 The author could first point out the current application of microRNA in cancer oncogenesis, diagnosis and therapy, and to increase importance and relevance of conclusion to the topic, whether microRNAs will be a potential diagnostic biomarker in endometriosis is the part to be more discussed.

We do recognize that current application of microRNA in cancer is a field of great interest and that research endeavours are being carried in order to understand the contribution of miRNAs in these malignancies. Nevertheless, this issue is far from the goal of the report submitted for publication in the WJOG and would deserve an individualized review. However, updated literature regarding the role of miRNAs as biomarkers of endometriosis has been discussed and concerns regarding current research in the field have been addressed in the discussion section.

Answers to comments by *reviewer 00742364*:

This is an interesting review article on a complex topic. The authors have done a good job compiling all the recent and compelling literature in the area. The main issue I have with the article is it doesn't seem to flow well for the reader. It's difficult to walk away with a sense of how this information can be used in the immediate term to drive research and clinical work. I offer specific comments below and suggestions to improve the flow are:

Thank you very much for your suggestions. An effort in order to increase clarity and comprehensibility has been made throughout the article and the specific points suggested have been addressed as follows:

1) ***Suggest expanding the first para of the Intro (Pg 5) to include more epidemiology/statistics of those with endometriosis (age of women at diagnosis, maybe some ethnic profiles if they are available).***

A sentence has been included in the first paragraph providing information about mean age patients at diagnosis.

2) ***Lines 69-70, Pg 6, suggest adding 2-3 brief sentences regarding abnormal miRNA expression specifically in gyn pathologies. These are so related to endometriosis, I think it's worth expanding a little bit here.***

   This information has been included in lines from 118 to 121.

3) ***Line 74, Pg 6, should be pioneering, not pioneer***

   The word pioneer has been changed to its correct form “pioneering”, as referee suggested.

4) ***Suggest moving the section on "peritoneal factors and endometriosis" up toward the front more, after the introduction and before miRNAs and endometriosis. It has a lot of background info on endometriosis being a multi-faceted disease and inflammatory process that would help the reader as they go through the review.***

The section “peritoneal factors and endometriosis” has been moved up, as suggested. We also believe that the background information described in this section will help to understand what is explained in the following sections of the review.

I also suggest adding a paragraph to this section that discusses briefly the role that endometriosis has in cancer--specifically that it is a risk factor for ovarian cancer. That info would help when the authors write in a later section about ovarian cancer.

As you suggested in previous comments, we have added information regarding miRNA expression in several gynecological pathologies in the “miRNA in endometriosis” section. However, recent reports point out that “the strongest evidence (for the association between endometriosis and ovarian cancer) seems to come from prevalence data”, that is, prevalence of endometriosis in women with ovarian cancer, and that “data also suggest a reduced risk of certain histotypes of ovarian cancer in women with endometriosis” (Guo SW, 2015. PMID: 26335131). On the other hand, Munksgaard and Blaakaer (PMID: 21742370) conclude “Endometriosis seems to be a precursor of epithelial ovarian cancer, especially clear cell and endometrioid adenocarcinomas. However, current evidence is insufficient to draw any definitive conclusions whether this association represents causality or the sharing of similar risk factors and/or antecedent mechanisms”. In our hands, none of the patients with endometriosis operated have later been diagnosed of ovarian cancer. In the view of this controversy, and deeply appreciating your comments, we do believe that the link between endometriosis and ovarian cancer deserves a more accurate discussion that is far from the purpose of this review. We definitely will take into account your suggestion for further review works.

5) Pg 9, line 155 "In a recent work" should be "in a recent publication"

The expression has been changed to as suggested.

6) Line 173, Pg 9: would delete definitely

The adverb “definitely” has been deleted following suggestions

7) Line 202, Pg 10 "apart from his" should be "apart from its"

The expression has been changed according to reviewer suggestions.

8) Line 213, Pg 11, add the before authors

The expression “authors” has been changed by “the afore mentioned authors”.

9) Biomarkers of Endometriosis section (Pg 11: Suggest moving this to the end, right before the Conclusion and calling it something like "Clinical Utility of miRNAs in endometriosis”.

This section has been moved and retitled as “Clinical utility of miRNAs as biomarkers of endometriosis”.

10) Lines 218-233, Pg 11: these lines need a little more English polishing.

We do appreciate your comments regarding the use of English in this paragraph. All the points have been adequately corrected following suggestions.

- ✓ ***Insert "the fact that" after despite in line 218;***
- ✓ ***"for a" in line 219 should be "of";***
- ✓ ***should in line 222 should be usually or typically,***
- ✓ ***"a certain degree of expertise from clinicians is necessary" should replace lines 222-223; and "it is a costly procedure" should replace the last part of the sentence.***
- ✓ ***Furthermore in line 224 should be deleted.***
- ✓ ***Line 229 has a sentence that is incomplete--"the prognosis and the risk of..."?;***

  We do apologize for this circumstance. The incomplete sentence has been replaced by “the prognosis and increases the risk of recurrence”.

- ✓ ***line 230, this should be these.***

11) Line 253 Suggest changing Anyhow to in any case.

The expression has been changed as recommended.

12) Line 267, Pg 13, change sensible to "specific"

The expression has been changed as recommended.

13) Line 306, Pg 14, Suggest moving "endometriosis, angiogenesis and miRNAs" section to come after the miRNA in endometriosis and retitle it something like "Potential Pathogenetic mechanisms of miRNA in Endometriosis"

This section has been moved to come after the “miRNA in endometriosis” section and has been retitled as “Angiogenesis-related miRNAs in endometriosis”.

14) Pg 15, lines 331-332 Change to "some authors suggest this mechanism may reduce..."

The expression “in keeping with some previously mentioned authors” has been deleted.

15) Pg 16, Conclusion: suggest expanding this section to include future research directions, and future directions for physicians who treat endometriosis.

As suggested by the reviewer, this section has been expanded and all the commented points have been taken into account.

***16) Suggest adding a table that summarizes the findings from the different section--something that lists the miRNAs involved and where they are found (endometrium, PF, etc) to easily give the reader a snapshot of the findings*.**

Please find the suggested table at the end of the paper.

Answers to comments by *reviewer 03270452*:

the author describled detailly the mRNA roles in the endometriosis, though the author cited many papers, but there were few recently new articles, and the aothors should more pay attentions to the molecular mechanisms

Thank you very much for your comments. We do believe that for some aspects of the review consolidated articles on a certain issue need to be used. However, and following your suggestions, recent literature has been added and some previous articles deleted, as is highlighted in the “references” section.