

Dear editors:

Thank you very much for your letter and the reviewers' comments for our manuscript entitled "Effect of intrauterine perfusion of granular leukocyte-colony stimulating factor on the outcome of frozen embryo transfer in patients with thin endometrium: a retrospective study" (Manuscript NO: 65649). The comments were valuable and helpful for revising and improving our paper and guiding the significance of our studies.

We have studied the comments carefully and have made corrections that we hope are met with approval. The revised portions are marked in red in the manuscript. The main corrections in the paper and responses to the reviewers' comments are as follows:

Reviewer(s)' Comments to Author:

Reviewer

Comments to the Author

This manuscript encompass an interesting reseach question, and presents some potential value including adequate sample size and statistical methods. The manuscript is globally well-written and scientifically sound. However I have some concerns which need to be addressed before publication. Major evidences on frozen blastocyst transfers should be incorporated in the discussion as they are highly relevant for the scopes of the study:

1. CRL of frozen vs fresh is greater in the first trimester; DOI:<https://doi.org/10.1016/j.fertnstert.2020.11.035>

2.uterine artery PI of frozen vs fresh is lower in the first trimester and across gestation; DOI: 10.1002/uog.21969

3.Ebryonic cryo/thawing does not seem to prevent preterm Birth in IVF pregnancies. doi: 10.1080/14767058.2020.1771690.

All evidences cited above (which I strongly reccoment citing and including in the discussion) suggest that IVF pregnancies probably have some elements working against placentation, endometrial receptivity and cardiovascular abnormalities. Moreover, all these issues might improved for frozen ET.

Response: Thank you for the comment. We have added the major evidences on frozen embryo transfers in the discussion in revised manuscript.(Line 1 of pages 1 through line 7 of pages 2 of the discussion section)

Reviewer

Comments to the Author

Therefore this is relevant ofr the scopes of the authors for which they propose a method to further improve endometrium. May the proposed method be more effective in fresh cycles? Add a short mention to this issue as a speculation in the discussion section.

Response: Thank you for the comment. In the fresh embryo transplantation cycle, the endometrium is generally thicker due to stimulation by ovulation therapy, and thin endometrium is relatively rare. It is not clear whether the use of G-CSF is more beneficial to the thin endometrium of the fresh embryo transplantation cycle. We have add a short mention to this issue as a speculation in the discussion in revised manuscript. (Line 1 through line 7 of pages 8 of the discussion section)

Reviewer

Comments to the Author

Another weak point is that the biological basis to promote the use of G-CSF on the endometrium is not highlighted enough in the background. Cite some biological evidences supporting the improvement of endometrium or the scopes of the current study on pregnancy outcome improvement.

Response: Thank you for the comment. We have added the biological basis to promote the use of G-CSF on the endometrium in the discussion in revised manuscript.(Line 6 of pages 6 through line 8 of page 7 of the discussion section)

Reviewer

Comments to the Author

What are the arguments against (bacterial or viral contamination of the cavity?) what are the arguments in favour (promotion of cell growth and maturation favouring embryo implantation?).

Response: Thank you for the comment. We have added the argument against and in favour of intrauterine perfusion of G-CSF on the endometrium in the discussion in revised manuscript.(Line 9 through line 21 of page 7 of the discussion section)

Reviewer

Comments to the Author

Are there differences between cleavage stage embryos and blastocyst as far as the scope of the study are concerned? Please add this data and subanalysis.

Response: Thank you for the comment. We have added the data of the differences between cleavage stage embryos and blastocyst in the result in revised manuscript.(Line 8 of pages 2 through line 4 of page 3 of the result section) Also we have added the tables. (Table 3 and Table 4) Similar results were obtained after subgroup analysis (in cycles with blastula transplantation or cleavage stage embryo transplantation). We have added a short mention to this issue as a speculation in the discussion in revised manuscript.(Line 3 through line 5 of page 5 of the discussion section)

Reviewer

Comments to the Author

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Response: Thank you for the comment. We have performed further language polishing.

Reviewer

Comments to the Author

The title is too long, and it should be no more than 18 words.

Response: Thank you for the comment. We have change the title named Effect of intrauterine perfusion of granular leukocyte-colony stimulating factor on the outcome of frozen embryo transfer.

Reviewer

Comments to the Author

The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Response: Thank you for the comment. We provided the approved grant application forms.

Yours sincerely,

Ming-Qing Li, M.D., Ph.D.