Peer Review File

Article information: https://dx.doi.org/10.21037/tp-23-234

Reviewer A

This study explores the interaction between eclampsia and IVF on the risk of PTB. A total of 2,880,759 eligible participants from the National Vital Statistics System (NVSS) database were enrolled in this retrospective cohort study in 2019. Univariate and multivariate LR models were utilized to assess the associations between eclampsia, IVF and PTB. The authors conclude that Eclampsia and IVF were associated with an increased risk of preterm birth and the coexistence of eclampsia and IVF increased the risk of preterm birth.

Major comments
I provide a list of constructive criticisms if the authors which to restructure their methodology and reattempt a submission.

Specific comments
1. I am not sure that the conclusion of the article is scientifically sound. Are the authors bringing forward the concept that eclampsia in women with IVF should be managed differently? I hope this is not their message. A good point would be to assess if preeclampsia and IVF together increase the risk of PTB as compared to preeclampsia in patients with spontaneous conception.
Response: We deeply appreciate your suggestion. This study found that Eclampsia and IVF might have a synergistic interaction on the development and process of preterm birth. In this cohort study, all information of participants were obtained from National Vital Statistics System (NVSS) database, we were unable to obtain information on patients' preeclampsia, which was a limitation of this study that we have described in discussion section. More research is needed in the future to assess the effect of preeclampsia and IVF on PTB.

2. Methods should be revised: eclampsia indicates delivery by all guidelines and studies. Therefore, it is obvious that eclampsia associates to PTB when occurring below 37 weeks. I would recommend repeating the analysis with association with any preeclampsia and preterm preeclampsia which are conditions that can be managed conservatively up to a certain extent whereas eclampsia indicates delivery. Therefore, there is such an extent of collinearity and clinical correlation that it useless to assess association of eclampsia and IVF to PTB: every guideline predicts association of

delivery when a case develops eclampsia. There is no way to manage conservatively the case, as it is an indication to delivery. This comment alone is enough to decline publication if not revises appropriately.

Response: Thank you for your comments. We have modified some content about this manuscript. Please see the revised manuscript.

3. The manuscript presents overall a wrong and simplistic presentation, and lacks of obstetric expertise is evident. I noted that all authors are affiliated to the neonatology unit. Are all of them competent in paediatrics? Were there some obstetricians? This should be clarified.

Response：We apologize for the description problems in the original manuscript. We have modified this manuscript.

4. The conclusions are somehow naïve. How can patients affected by the rare eclampsia pay more attention? Once the disease is evident PTB is guaranteed. This sentence of the conclusions should be revised "The findings indicated that IVF pregnant women with eclampsia should pay more attention to the risk of preterm birth". Patients with preterm preeclampsia or with increased risk of developing the disease should pay attention with preventive measures and increases antenatal surveillance.

Response：We apologize for the description problems in the original manuscript. We have modified this conclusion in the revised manuscript.

5. There are major information missing in the background/discussion. The risk of PTB <37 weeks in singleton pregnancies achieved after IVF/ICSI is significantly greater than that occurring in spontaneous conception. This is due to a multifactorial iatrogenic aetiology in which placental diseases are included (of which preeclampsia and eclampsia are major components). This concept should be implemented in the background/discussion (1)

Response: Thank you for your advice. We have added the content in Introduction section: A meta-analysis showed that the risk of preterm birth <37 weeks in singleton pregnancies achieved after IVF/ intra-cytoplasmic sperm injection (ICSI) was significantly greater than that occurring in spontaneous conception. This is due to a multifactorial iatrogenic etiology in which placental diseases are included (of which preeclampsia and eclampsia are major components) [1]. Please see the revised manuscript.

[1] Cavoretto PI, Giorgione V, Sotiriadis A, Viganò P, Papaleo E, Galdini A, Gaeta G, Candiani M. IVF/ICSI treatment and the risk of iatrogenic preterm birth in singleton pregnancies: systematic review and meta-analysis of cohort studies. J Matern Fetal Neonatal Med 2022;35:1987-1996.

6. The absence of a CL typical of IVF with frozen embryo transfer and egg donations associates with low uterine artery pulsatility and resistance and these pregnancies are both associated to higher extent of preeclampsia (2-4). The authors should assess the type of IVF if the transfer is from a fresh or a frozen-thawed cycle. This is a major issue and an essential covariate missing in the methods/results. All the IVF protocol should be disclosed carefully, it is completely reticent in the current form.

Response: We deeply appreciate your suggestion. We agree with you. The absence of a CL typical of IVF with frozen embryo transfer and egg donations associates with low uterine artery pulsatility and resistance and these pregnancies are both associated to higher extent of preeclampsia [1-3]. However, all information of participants were obtained from National Vital Statistics System (NVSS) database in this cohort study, we were unable to obtain information on patients' the type of IVF, which could be an essential covariate. We have described the limitation in discussion section. More prospective studies are needed to determine the interaction between eclampsia and IVF on the risk of preterm birth.

7. The discussion should be rewritten after having carried out the study with appropriate design and having seen the new results with preeclampsia besides the obvious finding on eclampsia.

Response: Thank you for your comments. We have modified some content about this manuscript. Please see the revised manuscript.

Minor

Preterm birth was defined as any delivery occurring before 37 completed gestational weeks.

References

1. Cavoretto PI, Giorgione V, Sotiriadis A, Viganò P, Papaleo E, Galdini A, Gaeta G, Candiani M. IVF/ICSI treatment and the risk of iatrogenic preterm birth in singleton pregnancies: systematic review and meta-analysis of cohort studies. J Matern Fetal Neonatal Med. 2022 May;35(10):1987-1996. doi: 10.1080/14767058.2020.1771690. Epub 2020 Jun 4. PMID: 32498576.

2. Cavoretto PI, Farina A, Gaeta G, Sigismondi C, Spinillo S, Casiero D, Pozzoni M, Vigano P, Papaleo E, Candiani M. Uterine artery Doppler in singleton pregnancies conceived after in-vitro fertilization or intracytoplasmic sperm injection with fresh vs frozen blastocyst transfer: longitudinal cohort study. Ultrasound Obstet Gynecol. 2020 Oct;56(4):603-610. doi: 10.1002/uog.21969. Epub 2020 Sep 11. PMID: 31909549.

3. Wiegel RE, Karsten MJH, Reijnders IF, van Rossem L, Willemsen SP, Mulders AGMGJ, Koning AHJ, Steegers EAP, Danser AHJ, Steegers-Theunissen RPM. Corpus

luteum number and the maternal renin-angiotensin-aldosterone system as determinants of utero-placental (vascular) development: the Rotterdam Periconceptional Cohort. Reprod Biol Endocrinol. 2021 Nov 4;19(1):164. doi: 10.1186/s12958-021-00843-9. PMID: 34732224; PMCID: PMC8567673.
4. Cavoretto PI, Farina A, Miglio R, Zamagni G, Girardelli S, Vanni VS, et al. Prospective longitudinal cohort study of uterine arteries Doppler in singleton pregnancies obtained by IVF/ICSI with oocyte donation or natural conception. Hum Reprod. 2020;35:2428–2438. doi: 10.1093/humrep/deaa235.

Reviewer B

1) First, the abstract is inadequate and needs further revisions. The background did not describe the clinical needs for assessing the combined effects of eclampsia and IVF. In the methods, please describe the inclusion criteria of subjects, follow up procedures, and diagnosis of preterm birth. In the results, please briefly describe the clinical characteristics of the study sample, and the incidence rates of preterm birth in subjects with eclampsia and IVF. The conclusion needs to be more specific for reducing the "the risk of preterm birth".

Response: Thank you for your comments. According to your suggestion, we have modified the content of Abstract section. Please see the revised manuscript.

2) Second, in the introduction of the main text, the authors did not have comments on the limitations and knowledge gaps of prior studies. They also did not explain why they hypothesized the interactive effects between eclampsia and IVF and what the potential clinical significance of this research focus is.

Response: Thank you for your suggestion. According to your suggestion, we have modified the content of Introduction section. Please see the revised manuscript.

3) Third, in the methodology of the main text, the authors need to describe the research design of this study, and the details of follow up procedures. In statistics, please describe how multiplicative or addictive effect between eclampsia and IVF was ascertained and analyzed.

Response: Thank you for your reviews. Please see the revised manuscript.