
November 12, 2021

Dear editor and reviewers,

We thank the editors for giving us the opportunity to revise the manuscript as well as the reviewers for their comments. In the revised manuscript, we have restructured our manuscript. We have rewritten the "Case Presentation" section and added the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text to the Guidelines and Requirements. And the manuscript has been thoroughly revised and edited by a native speaker. The original figure documents and the approved grant application form(s) are provided. Based on the instructions provided in your letter, we have carefully revised the manuscript by incorporating all the suggestions by the review panel. Appended to this letter is our point-by-point response to the comments raised by the reviewers. We hope this revised manuscript has addressed your concerns, and look forward to hearing from you.

Yours sincerely,

Anyong Yu.

Reviewer #1:

1) The conclusions section of the abstract should be rewritten. The authors wrote the follow-up and clinical outcomes in the conclusions instead of writing them in the case presentation. The conclusions should highlight the most important findings and clinical recommendations of the manuscript. While the case presentation should contain all the relevant information. Please revise the abstract accordingly.

Response:

Thank you for the valuable suggestions. We have restructured the conclusion section both in the main text (page 9, line 235-241) and abstract (page 2, 46-51) in the revised manuscript.

2) In the core tip and introduction sections, the term "embryo damage" is unclear since it is

not usually used by embryologists nor gynaecologists. It should be replaced with an appropriate medical term depending on the meaning the authors wanted to transmit. I recommend writing "abortions".

Response:

Thank you for pointing out this problem in manuscript. According to your suggestion, in the revised manuscript "embryo damage" was replaced by "abortions".

3) The case presentation section is not written appropriately. It is difficult to understand the exact timing of the events the patient had. This is mainly because the authors confused the patient's history with the current complaints. Besides, the authors did not adhere to the journal's guidelines in reporting the patient's case. I heavily recommend rewriting the case presentation section entirely taking into consideration the journal's guidelines and separating the past complaints from the current presentation.

Response:

We are very sorry for our incorrect writing in the case presentation section. The "Case Presentation" section has been rewritten and divided into several subsection as Chief complaints, History of present illness, History of past history, Physical examination, Laboratory examinations and other tests according to the Guidelines and Requirements(page 4-7, line 83-161). We have rewritten the Chief complaints, History of present illness, History of past history section (page 4-5, line 84-101).

4) In the case presentation section, the authors should clarify in the main text that the chromosome analysis was performed for both the blood cells and the villus tissue.

Response:

We have added the chromosome analysis was performed for both the blood cells and the villus tissue in the revised manuscript (page 6, line 157-161).

5) After a careful reading of the manuscript, I disagree with the authors about the conclusion "Two-chambered heart has deleterious effects on pregnancy". The authors mentioned that the patient was active and asymptomatic before pregnancy and after abortion, with cyanosis

episodes when crying and having cold (stress). This in turn demonstrates that the hemodynamic changes during pregnancy have deleterious effects on cardiac function. Additionally, poor cardiac function may lead to insufficient uterine perfusion and a subsequent abortion. This is my own interpretation of the patient's case, I suggest at least discussing it in the manuscript. If the authors agree with it, I suggest mentioning this in the conclusion section of the abstract and the main text.

Response:

We gratefully appreciate for your valuable suggestion and strongly agree with the view that Focusing the point of view the relationship between hemodynamic changes during pregnancy and deleterious effects on cardiac function are discussed (page 8, line 203-208) . We have also added this view in conclusion section of the abstract and the main text (page 2, line 47-51 and page 9,238-240).

6) The authors are missing an important citation that dates back to 1977. A case similar to this case reached the 25th week of gestation. Additionally, the authors of that correspondence agree with my postulation that pregnancy negatively affects cardiac function. I attached the paper to this review just in case the authors do not have access to the American Journal of Obstetrics and Gynecology (PMID: 556664).

Response:

We gratefully appreciate for your rigorous consideration and provide the helpful case. We have added this citation in the revised manuscript (page 7, line 190-191). To describe this issue in more detail, we have added text to the discussion (page 8, 203-209).

Reviewer #2:

1) Title is not clear in itself. *"Multiple miscarriages accompanied by two-chambered heart and total situs inversus in a female patient: A case report". I think it is better to rephrase as " Multiple miscarriages in a female patient with two-chambered heart and total situs inversus". You can modify on your own way too.*

Response:

We gratefully appreciate for your valuable suggestion. We have rewritten the title as “Multiple miscarriages in a female patient with two-chambered heart and situs inversus totalis”

2) *Abstract: conclusion needs to be written considering the key message that you want the reader to have.*

Response:

Thank you for the valuable suggestions. We have restructured the conclusion section in the revised manuscript (page 2, 46-51).

3) *Case Description: Line 80: It might be better not mention date of presentation as this will help to track the patient and break her confidentiality.*

Response:

Thank you so much for your advice and we have deleted the date of presentation.

4) *Line 82: check spelling “menelipsis”. Line 97 check spelling “shen”.*

Response:

We are very sorry for the spelling errors and we have revised in the revised manuscript.

5) *Was it a missed abortion or incomplete abortion? Please check the standard definition of these terms or other types of abortion and mention the one that suits the case.*

Response:

We thank the reviewer for pointing out this issue. Early pregnancy loss takes many different forms. In missed abortion, there is asymptomatic or ‘missed’ death of the embryo or fetus without sufficient uterine contractions to push out the products of conception. In contrast, threatened abortion is characterized by symptomatic, ‘threatened’ expulsion of the products of conception, yet the cervical os remains closed, and the embryo or fetus remains viable. Inevitable abortion is distinguished from threatened abortion by the presence of an open cervical os, indicating the ‘inevitable’ passage of the conception products. In incomplete abortion, there is an ‘incomplete’ passage of the products of conception through the cervical os. A detectable rise in urinary human chorionic gonadotropin (hCG) was found in this patient

three months before the visit. Intrauterine pregnancy was revealed, but no embryo or fetal vascular pulsation was detected by B-ultrasound. She did not follow advice of gynecologist to undergo further check until this visit. She denied abdominal discomfort and vaginal bleeding until five days prior to revisit. Then in hospital uterine aspiration was performed to absorb 8 g organized villus and 10 g decidual tissues. So, “missed abortion” may be more suitable as the diagnosis.

6) *Conclusion section is missing in the body of the manuscript. Please make a separate conclusion section. In conclusion, try to include key message of the study. limitations and recommendations.*

Response:

Thank you for the valuable suggestions. As you suggested that we have restructured the conclusion section in the revised manuscript (page 9, line 235-241).

7) *References need correction for upper cases/lower case, use of parenthesis, and other grammatical corrections.*

Response:

We have made correction on references according to your comments.

8) *Legend for figure 3 is lengthy. It is better to remove the part that is already mentioned in the body of manuscript.*

Response:

Legend for figure 3 have been simplified and the part that is already mentioned in the body of manuscript are deleted.

9) *Whole of the manuscript needs revision for use of proper English or else can be reviewed by a native English speaker. There are few punctuations errors too, which need correction.*

Response:

Thanks so much for your useful comments. We are very sorry for the mistakes in this

manuscript and inconvenience they caused in your reading. The manuscript has been thoroughly revised and edited by a native speaker. We have made correction on the punctuations errors. For example, “BP, 134/52 mmHg; heart rate, 137 beats/min; respiratory rate, 18 breaths/min; SPO2, 68%” are revised to “a blood pressure (BP) of 134/52 mmHg, a heart rate of 137 beats/min, a respiratory rate of 18 breaths/min, and 68% SPO2” , etc.

Reviewer #3:

This is a rare, interesting and well-documented case report.

Reviewer #4:

1) In "case summary" section, *"a birth history of cyanosis" is not a clinical presentation, and it's a personal history.*

Response:

We are so sorry for this mistake. We have rewritten the case summary section (page 2, line 37-44).

2) In "final diagnosis", the author concluded *" missed abortion due to Complex congenital heart disease.....". How to confirm the relationship? What is the possible mechanism for it?*

Response:

Thank you so much for pointing out this problem in manuscript. As suggested above, it is inappropriate to conclude the final diagnosis as “missed abortion due to Complex congenital heart disease.....”. We have modified the final diagnosis in the revised manuscript. The 30 to 50 percent increase in cardiac output is associated with pregnancy. The hemodynamic changes during pregnancy may have deleterious effects on cardiac function, and poor cardiac function may lead to insufficient uterine perfusion and a subsequent abortion in turn. That is to say that hemodynamic changes during pregnancy in patient with two-chambered heart and situs inversus totalis may lead to hypoperfusion and miscarriage.

3) *In this article, many sentences and expressions should be polished and modified by native English speaker. For example, "One day post-operation", "reported no medication use routinely", etc.*

Response:

We are very sorry for the mistakes in this manuscript and inconvenience they caused in your reading. The manuscript has been thoroughly revised and edited by a native speaker. Thanks you so much for your useful comments.