Response to reviewers

Reviewer #1:

1. The incidence of premature ovarian failure is gradually increasing, which is closely related to the physical and mental health of women. it is very necessary for early diagnosis and intervention of premature ovarian failure. this article comprehensively evaluates the oxidative stress in early ovarian failure and premature ovarian failure according to the oxidative stress and antioxidant potential in blood in order to determine the causes of premature ovarian failure. The possibility of oxidative stress and antioxidant potential as biomarkers of premature ovarian failure was studied, which has a certain clinical reference value for the early diagnosis and treatment of premature ovarian failure；

Response: **The authors would like to thank Reviewer 1 for his/her constructive critique to improve the manuscript. We have made every effort to address the issues raised and to respond to all comments. The revisions are indicated highlighted in the revised manuscript. Please, find next a detailed, point-by-point response to the reviewer's comments. We hope that our revisions will meet the reviewer's expectations.**

As the reviewer pointed out, there are no clear diagnostic criteria for POI, but in general the criteria are as follows:

1) Age < 40 years

2) Secondary amenorrhea (≥ 4 months)

3) FSH ≥ 40 mIU/mL or more (two or more measurements)

However, as this disease is progressive and irreversible, early diagnosis is required before the above symptoms appear. In this study, we examined whether the diacron-reactive oxygen metabolite test (d-ROM), which reflects oxidative stress and antioxidant capacity, and biological antioxidant potential (BAP), can be used as biomarkers for POI. In the future, as we have mentioned in the Discussion section of the revised manuscript, a comprehensive evaluation of blood d-ROMs and BAP at incipient ovarian failure (IOF) and transitional ovarian failure (TOF), which are the preceding stages of POI, would be conducted. Moreover, we plan to investigate whether they can be biomarkers for the early diagnosis of POI and pursue the possibility of early diagnosis and therapeutic intervention for POI.

2. In this paper, the method of clinical case analysis was used to analyze and evaluate the related indexes of oxidative stress and antioxidation in the blood of patients with premature ovarian failure and healthy women of the same age with normal ovarian function. The direction is new, but the number of detection indexes and samples is relatively small. In the later stage, we can continue to collect clinical data and expand the number of samples, so that the follow-up pathological mechanism research has a more solid foundation；

Response: **As the reviewer stated, the sample size used in our study was small. However, we intend to accumulate more cases and examine a larger sample size in**

the future and, at the same time, examine how this state of oxidative stress affects POI pathology. We have discussed this issue in the revised manuscript as follows: "This study was limited by the small sample size. However, as the number of target cases in this time was small, we will continue to accumulate and examine a larger sample size in the future and investigate how the state of oxidative stress in the blood and local factors, such as a decrease in the number of remaining follicles associated with ovarian dysfunction and a decreasein egg quality, affect POI pathogenesis."

3.Some charts can be added to make the expression of the article more diverse；

Response: **Based on the reviewer's recommendation, we have created a chart describing the characteristics of the study participants.**

4.The conclusion is too simple to clarify the main points of the whole article, and there is no research significance or deeper discussion.

Response: **The cause of POI is largely unknown. However, regardless of the cause of this disease, which may be attributed to early follicle depletion, inhibition of follicular development, etc., the number of remaining oocytes/follicles is extremely low or may have been completely absent. It has been suggested that mitochondrial function in oocytes and cytotoxicity caused by reactive oxygen species are factors responsible for the decrease in the number of remaining follicles due to the decline in ovarian function with aging and the deterioration in oocyte quality. In this study, we used d-ROM and BAP to assess oxidative stress and examined whether they could be biomarkers for POI. In our study, oxidative stress (d-ROMs, OSI) levels were significantly higher in the POI group than in the control group, suggesting that the oxidative stress state may be not only a factor in POI, but also a biomarker of POI. In the future, we plan to accumulate and examine cases and, at the same time, investigate which part of the pathology in POI is affected by this state of oxidative stress. Furthermore, a continuum of ovarian function decline is observed in POI. First, an incipient ovarian failure (IOF), then a transitional ovarian failure (TOF), and then a transition to POI. Moreover, as the disease is progressive and irreversible, it presents with early ovarian failure before progression to POI. We plan to investigate whether the d-ROM and BAP examined this time can be biomarkers for early diagnosis in IOF. Therefore, we believe that our findings are of great significance as they suggest that d-ROMs and BAP can be used as biomarkers for POI.**

Reviewer #2: 20 January 2023 Review report on the manuscript titled 'The importance of oxidative stress and antioxidative potential in premature ovarian insufficiency' by Kakinuma K & Kakinuma T, submitted to World Journal of Clinical Cases Manuscript ID: 83009 Dear Authors, In the present manuscript entitled 'The importance of oxidative stress and antioxidative potential in premature ovarian insufficiency', Kakinuma and Kakinuma studied the oxidative stress of diacron-reactive oxygen metabolites and biological antioxidant potential in premature ovarian insufficiency (POI). The main strength of this manuscript is that it addresses an interesting and timely question, revealing that oxidative stress was significantly greater in the POI and thus, oxidative stress is a potential biomarker in POI. In general, I think the idea of this editorial is really interesting and the authors' fascinating observations on this timely topic may be of interest to the readers of World Journal of Clinical Cases. However, some comments, as well as some crucial evidence that should be included to support the authors' argumentation, needed to be addressed to improve the quality of the manuscript, its adequacy, and its readability prior to the publication in the present form. My overall opinion is to publish this manuscript after the authors have carefully considered my suggestions below, particularly expanding the body of the manuscript by adding more evidence. Please consider the following comments:

1. Title: I recommend that the authors present the title concise, self-explanatory, and stating the most important message of this manuscript. If possible, please avoid using abbreviation in the title.

Response: **The authors would like to thank Reviewer 2 for his/her constructive critique to improve the manuscript. We have made every effort to address the issues raised and to respond to all comments. The revisions are indicated highlighted in the revised manuscript. Please, find next a detailed, point-by-point response to the reviewer's comments. We hope that our revisions will meet the reviewer's expectations.**

In accordance with the reviewer's suggestion, we have revised the title as follows: "Analysis of oxidative stress and antioxidative potential in premature ovarian insufficiency"

2. Abstract: Please present the abstract with 200-250 words and proportionally present the background, the objectives, the short summary, and the conclusion. The background should include the general background (one to two sentences), the specific background (two to three sentences), and current issue addressed to this special issue (one sentence). The end of the result should include one to two sentences which put the result into a more general context. The conclusion should include one sentence describing the main message using such words like "Here we show", the potential and the advance this article has provided in the field, and finally a broader perspective (two to three sentences) readily comprehensible to a scientist in any discipline.

Response: **Please note that we have revised the Abstract on Page 3, 4 according to the reviewer's suggestion.**

3. Keywords: Please list relevant six keywords according to the journal's guideline and

use as many keywords as possible in the first two sentences of the abstract.
Response: **Please note that we have added some keywords to the revised manuscript on Page 4.**

4. Introduction: This section is well written and nicely presented, summarizing POI and presenting the short summary of the following sections. Nevertheless, I recommend that the authors present and clarify the background, the specific background, and the current issue addressed to this article, leading to the objectives. I recommend that the authors abridge the general background, focusing on the constructs contributing to the specific background. For this purpose, the introduction is expected to provide the main constructs of the topic, which should be acknowledgeable to a reader in any discipline, so that the authors make this section persuasive enough to put forward the main purpose of current research the authors conduct and the specific purpose the authors have intended by this article. Thus, I expect the authors to present PIO, oxidative stress, and the current issue in a cohesive sequence.
Response: **As the reviewer pointed out, POI is majorly a disease of unknown cause, causing problems, such as intractable infertility.**
In POI, regardless of the cause, the number of remaining oocytes/follicles is extremely low or completely disappears due to early follicle depletion and inhibition of follicular development.
Oxidative stress reportedly causes various diseases, and mitochondrial function in the ovum and the accompanying reactive oxygen species have been suggested to be involved in cytotoxicity. Therefore, we decided to evaluate the oxidative stress status of the blood of patients with POI. Conventional measurement of active oxygen is complicated; however, in this study, by using d-ROMs and BAP, which can easily evaluate the state of oxidative stress, we investigated whether these could be biomarkers for POI.
Please note that we have made the appropriate revisions in the Introduction.

5. Methods: I suggest citing more references to ensure the reliability and the integrity of evidence in study design the authors have decided to build and methodology they have applied.
Response: **In accordance with the reviewer's suggestion, we have cited more references in the Materials and Methods section on Pages 8 and 9.**

6. Results: I recommend that the authors present a table presenting all statistical values.
Response: **Since the p-value was very small, we have stated that the *P*-value was <0.001.**

7. Discussion: After the short summary of the results detailed in the previous sections, I recommend that the authors fully develop this section by focusing on the current issues addressed to this review. I suggest, toward the end of this section, clearly stating the potential of this study complementing as the extension of the previous understanding, the implication of the authors' opinion, how this article could facilitate future research,

the ultimate goal, the challenge, the knowledge and the technology necessary to achieve this goal, the statement about this field in general, the importance of this line of research, and the limitation and the weakness of this study which have emerged on the surface in the course of this study and in translational applicability.

Response: **As the reviewer mentioned, the number of cases covered in this study was small; hence, we have stated that we intend to accumulate more cases and examine a larger sample size in the future. Our future studies and goals have been described in the Discussion section. If oxidative stress status can be evaluated as a biomarker even at this stage, we believe that early POI diagnosis and intervention for early treatment will become possible.**

8. Finally, I believe that the manuscript would benefit from presenting a paragraph of conclusion, if the authors explain the theoretical implication as well as the translational application of this research by adequately conveying what they believe is the take-home message. I believe that it would be necessary to discuss theoretical and methodological avenues in need of refinement, as well as suggestions of a path forward in transplantation research.

Response: **The message we intended to convey in the Conclusion section is that the evaluation of oxidative stress (d-ROMs, OSI) in POI can be a biomarker for this disease; evaluation of d-ROMs and OSI may be useful for early intervention in POI treatment, including infertility treatment.**

9. Figures: Please present the figures in color.

Response: **Please note that we have revised the figures accordingly.**

10. References: I recommend presenting more references to ensure the reliability and the integrity in evidence that the authors develop the arguments in this editorial. Typically, a manuscript like this cites more than 60-70 references. Overall, the manuscript contains five figures, one tables, and 46 references.

Response: **In accordance with the reviewer's suggestion, we have cited more references in the revised manuscript, including POI, d-ROM, and BAP testing.**

I believe that this manuscript may carry important value in investigating oxidative stress as the pathogenesis of POI. After careful revision, I hope that the manuscript can meet the journal's high standard for publication. I declare no conflict of interest regarding this manuscript. Best regards, Reviewer

Response: **We have followed your recommendations and revised the manuscript accordingly. We hope that our revisions will meet the reviewer's expectations and that the revised manuscript is now suitable for publication in *World Journal of Clinical Cases*.**

Reviewer #3: First of all, it is a well-written and organized paper. This paper is demonstrating the important role of the oxidative stress, which is a probable cause of many diseases and disorders, including POI. Consequently, this could mean the possible utilization of the oxidative stress occurrence as a biomarker for the early detection/prevention and treatment of POI.

Response: **The authors would like to thank Reviewer 3 for his/her constructive critique to improve the manuscript. We are grateful for your positive feedback.**