

March 17, 2017

Godefridus J. PETERS MD.

Editor in Chief,

World Journal of Clinical Oncology

Dear Dr. Peters,

Thank you for the careful evaluation of our review manuscript entitled “**Current State and Controversies in Fertility Preservation in Women with Breast Cancer**”. We have meticulously considered and addressed each reviewer’s comments. We would like to thank the reviewers for their invaluable comments and suggestions.

Thank you again for giving consideration to our manuscript.

Kind regards,

Kutluk Oktay M.D., PhD., FACOG

1. Innovation Institute for Fertility Preservation and In Vitro Fertilization, 4 Columbus Circle, New York, 10019, NY, USA.

2. Laboratory of Molecular Reproduction and Fertility Preservation, Department of Obstetrics and Gynecology, New York Medical College, Valhalla, 10595, NY, USA.

Editor's Comments to Author(s):

1. "Please highlight the changes made to the manuscript according to the peer-reviewers' comments."

Response 1: We have revised our article and highlighted all the changes made in the manuscript according to the reviewers' suggestions.

2. "Please provide the approved grant application form(s)."

Response 2: As our manuscript is a review article we have decided to exclude grant information from our manuscript.

3. "Please list 5-10 keywords for each paper, which reflect the content of the study and are selected mainly from the *Index Medicus*. Each keyword is to be separated by a semicolon."

Response 3: We have rewritten the keywords according to editor's suggestion.

4. "Please write a summary of no more than 100 words to present the core content of your manuscript, highlighting the most innovative and important findings and/or arguments. The purpose of the Core Tip is to attract readers' interest for reading the full version of your article and increasing the impact of your article in your field of study."

Response 4: We have added the Core Tip to the manuscript as suggested.

5. "In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article."

Response 2: We have made the Audio Core Tip for our article and submitted as suggested.

Reviewers' Comments to Author(s):

Reviewer 1

Reviewer's Number ID: 02104609

Comments to the Authors

1. "A well written review article for WJCO."

Response 1: We thank the reviewer for this encouraging comment.

Reviewer 2

Reviewer's Number ID: 00742054

Comments to the Authors

“Thank you for writing an interesting review article on this important issue! Please see my comments on the attached manuscript. Thank you and best of luck!”

1. “The 1 million primordial oocytes are present at birth. However, chemotherapy is usually done later in life when the number of primordial oocytes has dramatically reduced. Thus, it won't affect the entire 1 million oocytes. I think it would be better if the authors add the number of primordial oocytes at different stages of life, ie. puberty, young adulthood, etc. this will show the vital impact of chemotherapy on the smaller number of remaining primordial oocytes”.

Response 1: We thank the reviewer for the useful suggestion. We have added to the revised manuscript the information regarding the possible use of robotic surgery in uterine transplantation with 2 citations from the literature.

2. “This sentence needs appropriate Reference.”

Response 2: We appreciate the reviewer's recommendation and we have added two references to the sentence.

3. “This is the first time that the “AC” is used. Do you mean “adjuvant chemotherapy”? If yes, please write the entire words here and then later use ‘AC’.”

Response 3: We thank the reviewer for the question. This chemotherapy regimen is commonly used in breast cancer and named as AC regimen. In this sentence AC stands for Doxorubicin (Adriamycin) and Cyclophosphamide, as it is mentioned in the parenthesis.

4. “What do you mean by “lack of placebo”? Does it mean that the studies did not use placebo in

patients requiring chemotherapy? If yes, I do not think this would be a shortcoming of the studies as it is not ethical not to give treatment to the cancerous patients who need appropriate chemotherapy. I suggest you remove this.”

Response 4: We thank the reviewer for the question. This sentence is written under the section of the controversial use of GnRH agonists to prevent chemotherapy-induced ovarian damage. In this sentence, “lack of placebo” is used to raise the concern about the studies that did not have placebo control for GnRH agonist, not for chemotherapy.

5. “What are the success rates of Cryopreservation of mature or immature oocytes? Are they different at different maternal age? It will be interesting to the readers to see the rates and compare them with the rates Embryo cryopreservation.”

Response 5: We appreciate the reviewer’s recommendation. To provide more information we added the following sentence with a citation in the manuscript; “Oocyte cryopreservation success rates vary depending on age, number of oocytes frozen and the freezing protocol. In a recent individual patient data meta-analysis we calculated these success rates ^[48]. (An interactive online success rate estimator can be found online at <http://fertilitypreservation.org/index.php/probability-calc>)”

6. “This paragraph needs appropriate Reference.”

Response 6: We appreciate the reviewer’s recommendation and we have added references as suggested.

Reviewer 3

Reviewer’s Number ID: 00181208

Comments to the Authors

1. “This is a useful brief review. I would suggest adding a table with the different fertility options discussed and advantages –disadvantages as well as efficacy rates and established versus experimental status. Another table with specific regimens and doses of ovarian stimulation for IVF would be of interest. Addition of the risk of sterility with specific regimens used in breast cancer (to supplement the information given in table for individual

drugs) and comparison with regimens used in other cancers such as lymphoma (also a common practice problem in oncology) would be desirable as a comparative reference. A couple of typos: -p. 7 line 5 should be: "...is shown not to be the case." -P. 11 last sentence of 3rd paragraph is not clear what it means that the letrozol-gonadotropin protocol is associated with DFS. Please clarify."

Response 1: We thank the reviewer for the encouraging comments and suggestions. We have added 2 new tables (Table 2 and Table 3) to the manuscript according to the reviewer's suggestions.