Author’s response to reviews

Title: Cancer and fertility preservation: international recommendations from an expert meeting

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RESPONSES TO EDITORIAL AND REVIEWERS’ COMMENTS

EDITORIAL COMMENTS
1. Please include the funding information in the Acknowledgements section rather than Competing interests

Reply (R) 1. Done; as suggested, we have moved the funding information in the Acknowledgements: “This work was partially supported by a grant from the Associazione Italiana per la Ricerca sul Cancro (AIRC; investigator grant number: 2013-14272) and by a grant from the Italian Ministry of Health (Centro Nazionale per la Prevenzione e il Controllo delle Malattie, CCM project, approved by D.M. 05/03/2012). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript”.

2. We suggest an alternative title might better reflect the contents of your correspondence article: "Cancer and fertility preservation: international recommendations from an expert meeting".

R2. Done, modified as suggested.

REVIEWERS’S COMMENTS

Reviewer #1:

This paper is an expert opinion piece regarding 10 'hot topics' in fertility preservation in cancer patients. The authors convened a workshop including European experts in oncofertility in Genova, Italy in April 2015. The proceedings of this meeting have been summarized in this paper and final review was performed by a U.S. expert as well.

Comments:

Topic #2, page 8, line 53: "increasing pregnancy rates over time thus confirming the success of the strategies for fertility preservation": I disagree with this conclusion. There is ample evidence to suggest that even after highly intensive alkylator and radiation based therapies such as myeloablative hematopoietic cell transplantation, it is possible to recover spermatogenesis. Hence, increasing pregnancy rates with increasing time since therapy may not be solely attributable to fertility preservation techniques; it may simply reflect recovering gonadal function.

R3. As suggested by the Reviewer, we have deleted the sentence “thus confirming the success of the strategies for fertility preservation”.

Topic #4, page 12, line 11: "Are cryopreservation strategies accepted ...": Please change this to "Are gamete and embryo cryopreservation strategies accepted ...". As currently written, it's unclear whether you are also including ovarian or testicular tissue cryopreservation.

R4. Done, modified as suggested.
some authors suggest to propose cryopreservation of ovarian tissue to all patients who cannot delay the initiation of cancer treatments. I disagree with this statement, because many of the patients who cannot delay anticancer treatments are those with aggressive hematologic malignancies. Significant controversy exists regarding the potential for malignant contamination of ovarian tissue in this population, and hence, ironically, those who would most benefit from a rapid technique to preserve fertility are the very patients in whom it may pose a great risk.

R5. As suggested by the Reviewer, we changed the sentence “For these reasons, some authors suggest to propose cryopreservation of ovarian tissue to all patients who cannot delay the initiation of anticancer treatments [111]” to the new sentence “For these reasons, cryopreservation of ovarian tissue can be proposed to selected patients who cannot delay the initiation of anticancer treatments [111]”. Then, we have discussed the possible risk of ovarian tissue malignant contamination, especially in patients with aggressive hematologic malignancies “Therefore, patients diagnosed with cancer with a high risk of malignant contamination to the ovaries (e.g. aggressive hematologic malignancies) and with no reliable molecular markers for a pre-transplantation examination may be not eligible for ovarian tissue auto-transplantation [118].”

Topic #8, page 22, line 48: As mentioned above, I feel it is essential to clarify that ovarian tissue cryopreservation has an extremely high risk of contamination with malignant cells in leukemia patients and thus this technique is not safe in these patients. Even high sensitivity approaches to detect minimal residual disease such as flow cytometry and PCR are not guarantees to prevent reimplantation of malignant tissue. Most studies discussing tissue cryopreservation are clear that this should not be used in patients with blood cancers (although the lymphoma risk may not be as high as leukemia).

R6. As suggested, we have added a sentence to Recommendation 8 to clarify the possible risk of contamination with malignant cells in leukemia patients: “Patients with cancer with a high risk of malignant contamination to the ovaries (e.g. aggressive hematologic malignancies) should not be considered eligible for ovarian tissue auto-transplantation (V, B)”.

Minor comments:

Abstract, line 26: "should be often faced" - change to "should be addressed"

R7. Done.

Background, page 5, lines 6-7: "thousands of girls, young women and men" - change to include boys, or just say young women and men, or young male and female patients

R8. Done.

References, page 38, reference 102 is a duplicate of reference 78.
R9. As suggested, we have changed reference 102 to reference 78.

Reviewer #3:

This is a thoughtful and thorough discussion of fertility for cancer survivors. There are a few areas that need revision or correction:

1. On page 9, the last paragraph needs to be more clear and expanded. Explain the high induced abortion rates.

R10. As we have mentioned, there seems to be a high induced abortion rate in breast cancer patients: “However, high induced abortion rates have been observed in patients who became pregnant after breast cancer diagnosis reaching as high as 30% [23,30,31].” Possible explanations are that breast cancer patients achieved pregnancies at older age than women in the general population and that the altered hormone profile due to breast cancer treatment might be less able to support a pregnancy. Moreover, in the available published papers, it is not always clear if the abortion was a miscarriage or an induced abortion (e.g. induced for mistaken beliefs on its positive therapeutic role). However, due to the limited and controversial information on this topic, we prefer not to discuss this issue in the present manuscript.

2. On page 10, line 55, add that it has a direct effect during treatment only.

R11. As suggested, we have specified that the direct effect occurs during treatment only: “Finally, endocrine treatments used in breast cancer patients have both a direct and indirect effect on fertility and ovarian function: the direct effect, occurring during treatment only, is due to an impairment in ovulatory and endometrial functions, while the indirect effect is associated with the delay to conception that allows ovarian aging”.

3. On page 10, explain why tamoxifen needs 3 months to be out of the patient's system. Tamoxifen is sometimes used as a fertility medication, so what data show that there needs to be a 3 month delay? The bigger question is how long to wait after adjuvant chemotherapy.

R12. Available data suggest that tamoxifen might be teratogenic if given during organogenesis or, more in general, during pregnancy, being associated with different types of malformation: for this reason, it is considered safer to have a wash-out period before allowing a patient to become pregnant after exposure to tamoxifen as adjuvant treatment. However, tamoxifen is used also for controlled ovarian stimulation during oocytes/embryos cryopreservation, and the time between the last dose and embryo transfer might be shorter than 3 months. According to the suggestion of the Reviewer, to avoid confusion and due to the limited information on this issue, we have changed the sentence “(e.g. 3 months after tamoxifen completion) [9]” to the new sentence “(i.e. up to 3-6 months following the last administered dose) [11]” of anticancer treatment more in general (i.e. chemotherapy, tamoxifen etc), as specified in the ESMO guidelines.
4. On page 12, change that sperm cryo can be performed in many (not just "several") centers.

R13. Done.

5. On page 19, use low "concentration" instead of "amount."

R14. Done.

6. On page 19, reword the sentence to "Irrespective of which method is used, the success rates are best in women under 36, although success has been reported up to age 44 with vitrification."

R15. Done, modified as suggested.

7. On page 19, line 48, reword the last sentence in the middle paragraph to "increasing use of vitrification in infertile couples and by 2010, vitrification..."

R16. Done, modified as suggested.

8. On page 20, line 2, start a new sentence: "Pregnancy rate after embryo thawing is strongly dependent on age, ranging from over 40% in women younger than 35 to less than 20% in women over 40."

R17. Done, modified as suggested.

9. On page 20, middle paragraph, it is "fact" not "facts" and add "when" analyzing

R18. Done, modified as suggested.

10. On page 20, it is a "particular" protocol (not "peculiar")

R19. Done, modified as suggested.

11. On page 22, it is "any" time in the menstrual cycle (not "every")

R20. Done, modified as suggested.
12. On page 22, second paragraph, add egg collection is not recommended "in patients who have received recent chemotherapy, owing to ..."

R21. Done, modified as suggested.

13. On page 22, recommend saying "... cryopreservation is strongly dependent upon the patient's ovarian reserve. For this reason, patients over 40 or with reduced ovarian reserve are not good candidates." (Your reference is about age >40)

R22. Done, modified as suggested.

14. On page 24, last sentence: it should be "Of note is that in..."

R23. Done, modified as suggested.

15. On page 25, in patients undergoing COS, LHRHa can be given after the retrieval to avoid a flare. It seems best to give it before any chemotherapy and not wait until the second chemotherapy cycle.

R24. According to the suggestion of the Reviewer, we have deleted the sentence “In these cases, to avoid the flare-up after COS and the consequent possible side effects, LHRHa should be administered before the second chemotherapy cycle instead of before the initiation of the gonadotoxic treatment”.