Author's response to reviews

Title: Alternative and antioxidant therapies utilization by a sample of infertile males in Jordan: a cross sectional survey

Authors:

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Author's response to reviews: see over
Dear Sir,

Thank you for your letter, dated 30th-April-2014, concerning the manuscript entitled “Alternative and antioxidant therapies utilization by a sample of infertile males in Jordan: a cross sectional survey”. The author studied your comments carefully and made major corrections, which she hopes would meet with your approval. Please consider my point-by-point responses to the reviewers in the following text.

* Title changed in response to Reviewer 1 point
Comments of reviewer 1:

1. My main concern is with the age of some of the references in this paper. Many of the articles cited in the introduction are 10 to 15 years old and there are more recent references that could and indeed should be used to support the text. For example, in paragraph 2 the authors state 'Recent studies demonstrate that elevated levels of ROS....' these papers were in fact published in 1995 and 1997 and are therefore not recent. The paper would benefit significantly by an up to date introduction.

Our response: The author would like to thank the respected reviewer for this rightful point. Thirteen references were updated to manifest more recent studies from the literature. The author agrees with the reviewer that an updated introduction will better support the manuscript, and thus the following references replaced the old references in the manuscript:


In addition, the statement that was referring to old references in Page 3, Paragraph 2, was modified into:

“Several studies demonstrate that elevated levels of ROS are detected in the semen of 25% to 40% of infertile men (7, 12, 13)”.

2. There are some sections of the paper that require some minor revision due to missing words or difficult sentence structure or grammatical errors.

Our response: The author does appreciate the reviewer’s suggestion to improve the language of the manuscript. Major issues in English language were avoided in the revised manuscript. The author hopes that the revised manuscript will meet with the respected reviewer’s approval.
3. The authors do not seem to be aware of the Cochrane systematic review Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Antioxidants for male subfertility. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD007411. DOI: 10.1002/14651858.CD007411.pub2. which currently includes 34 randomised controlled trials of 2876 couples with subfertility. Although none of the trials are from Jordan there are trials from Kuwait, Iran and Saudi Arabia. This review should be acknowledged.

Our response: The author would like to thank the respected reviewer for pointing out this valuable reference. Indeed, this systemic review on antioxidants and male subfertility strengthens the study findings and conclusions. Therefore, this review was acknowledged in the text and cited in the following places:

Page 11, para 1, line 6
Page 11, para 1, line 8
Page 12, para 1, line 6
Page 12, para 1, line 8
Page 13, para 1, line 13

4. The authors have clearly described the settings and inclusion criteria and summarized the demographics. It is unclear if all eligible men in the settings were approached to participate and this needs to be clarified by the authors.
Our response: Yes, indeed. The author stated in the manuscript, page 5, that only male patients attending the study centers were invited to participate in the study:

“Only male patients attending any of the study centers were invited to complete the questionnaire”

Then, in the Results section, page 6, para 2, the author stated that “A total of 500 questionnaires were distributed, out of which 428 were completed (response rate = 85.6%).”

We hope that this will clarify the point.

5. In the methods section 'the study population was then segregated...' would be better rephrased as 'the study population was then subgrouped...'

Our response: Sentence was rephrased into: “The study population was then subgrouped into two groups, Group A and Group B.”

6. In the results section it would be useful to see if there were any statistical differences between the age groups and if so between which groups.

Our response: As stated in the Results section of the manuscript, study participants were mostly in the middle age class; 31-45 years (82%, n=428). In addition, more than two thirds of the participants who used alternative and antioxidant therapies (n=184), as infertility treatment aid, were older than 36 years. Figure 1 illustrates the prevalence of alternative and antioxidant therapies use for infertility treatment among study participants by age group. The prevalence of alternative and antioxidant therapies considerably decreased in younger ages; as clearly
demonstrated by Figure 1. Upon statistical analysis, there was no significant difference in the alternative and antioxidant therapies utilization between age groups of 18-25 and 26-30 or between age groups of 36-40 and 41-45. However, there was a significant difference between age groups of (18-25, 26-30, 31-35) and (36-40, 41-45). The author chose not to complicate the discussion with this analysis and generalized that the prevalence of alternative and antioxidant therapies considerably decreased in younger ages. Nonetheless, when we compare the prevalence of alternative and antioxidant therapies among participants of advanced age group (more than 46 years) to the middle aged groups (36-45), the tendency to use alternative and antioxidant therapies significantly drops. To reflect this on the analysis, the following statement was added to the manuscript, Page 7, para1, line 1-4.

“On the other hand, interest in alternative and antioxidant therapies for infertility treatment also diminished in participants of advanced ages (more than 46 years), suggesting a correlation between age factor and the propensity to use alternative and antioxidant therapies for infertility treatment.”

7. In the results section the values in brackets referring to the number of respondents in each group is very confusing as it is not a direct reference to the preceding % of respondents to a question in the survey. e.g. only 79 (32%, n=244) of Group B. These may be better rewritten as 'only 32% (79/244) of Group B'

Our response: Point was acknowledged in the revised manuscript and the presentation of numbers and percentages were accordingly modified throughout the manuscript.
8. As the ultimate goals of these couples is a live baby it would be of interest to have the reported pregnancy rates for Groups A and B if this data is available to the authors.

**Our response:** We agree with the respected reviewer on the importance of this interesting data. It is stated in the manuscript that: “When Group A participants were asked whether the alternative and antioxidant therapies used for their infertility were actually helpful to enhance their fertility, only 17% (31/184) of Group A participants reported that there were positive outcomes associated with the alternative and antioxidant therapies utilization. However, only 6.5% (2/31) of those participants could relate the reported positive outcomes to increased pregnancy rate. Rather, 93.5% (29/31) of the participants related the reported positive outcomes associated with their utilization of alternative and antioxidant therapies to general health status enhancement.”

In regard to Group B, infertile males who don’t use alternative and antioxidant therapies for their infertility treatment, the survey questions were structured in a way that only Group A participants would have the chance to answer the questions about alternative and antioxidant therapies effectiveness, thus, Group B participants were not eligible to answer these questions.

In addition, since this is a cross section survey that is based on a single time response from the interviewed patients at the study centers, it is hard to follow up on the pregnancy rate or live births for these patients after conducting the interview. Moreover, all Group A patients were simultaneously on dual therapies; conventional medical therapies and the declared alternative and antioxidant therapies. Therefore, it would be hard to conclude whether any increased pregnancy rate is directly related to the utilization of alternative and antioxidant therapies.
9. The final sentence of the results section is not clear and needs further clarification. Are the authors referring to pregnancy or something else?

**Our response:** The author was indeed referring to the pregnancy rate. The statement was modified to better clarify this:

“Apparently, such belief in effectiveness of alternative and antioxidant therapies was not supported by any kind of evidence, related to an increase in pregnancy rate, reported among Group A participants.”

10. In the discussion again there is some wording that may need to altered to improve readability.

**Our response:** The author revised the manuscript carefully to improve its readability.

11. In the discussion paragraph 2 the authors refer to 'numerous clinical trials' but only reference one. This is where the authors may want to refer to the Cochrane review.

**Our response:** Point was acknowledged and the pointed reference was cited to support the statement. The statement was modified into the following:

“Numerous clinical trials have investigated the potential role of antioxidant therapy to relieve ROS- induced male factor infertility (23)” Where reference 23 is the *Cochrane review.*

12. I am not sure if the paragraph beginning 'the human body employs three general tactics...' adds anything to the discussion or if it would be better placed in the introduction.

**Our response:** The author thinks that this paragraph introduces the discussion on the use of antioxidants, such as vitamins C and E, and comes in a sequence that allows the reader to easily
connect the introduced knowledge with the discussion part related to the results concerning these antioxidants.

13. The authors state that there is a need for physicians to become more aware of alternative and antioxidant therapies. This is indeed the primary purpose of the Cochrane systematic review that summarizes randomized controlled trial evidence. I acknowledge that access to the Cochrane Library is not available in all countries but the contact authors of reviews are able to provide copies to interested parties.

Our response: The author is grateful to the respected author for this suggestion. Indeed, this is a valuable source of information that must be acknowledged, not only in this study but also in any other related study. The reference was cited in the text to support the conclusions of this study (Page 13, para 1, line 13)

14. Diabetes is misspelt in Figure 5a, Effectiveness is misspelt in Figure 6

Our response: The author regrets for these mistakes and would like to thank the respected reviewer for pointing them out. Spelling was corrected in the figures.
**Discretionary revisions**

1. I suggest that the authors change the wording of the title so that cross-sectional study becomes cross-sectional survey to better reflect the content of the article

**Our response:** Point was acknowledged and the title wording was changed into “Alternative and antioxidant therapies utilization by a sample of infertile males in Jordan: a cross sectional survey”

2. I think that the word survey would be better suited than questionnaire. The paper does appear to be reporting on a simple survey of use of alternative and antioxidant therapies and does not appear to conduct any pre-testing of reliability and validity of the questions themselves and there is no statistical testing of the rigor of the questionnaire in the analysis which is mainly descriptive statistics.

**Our response:** with all due respect to the reviewer’s point of view, the author still thinks that the use of the word “questionnaire” in the manuscript is justified. The term “questionnaire” in this manuscript is referring to the survey conducting method rather than to a pre-tested study model.
**Comments of reviewer2:**

1. *Please have another native English speaker review your Results section prior to publication. In several areas the wording in this section is awkward*

**Our response:** The author would like to thank the respected reviewer for the valid suggestion to improve the manuscript’s language. We did our best to avoid major issues in English language in the revised manuscript. We hope that the revised manuscript will meet with the respected reviewer’s approval.

2. *Consider adding a section reflecting upon the use of selenium and zinc to page 11 or 12*

**Our response:** Although this would enrich the manuscript content, the author thinks that such elaboration might broaden the manuscript scope and volume. To avoid this caveat, the author chose to discuss and elaborate on the most commonly utilized forms of alternative and antioxidant therapies reported in the study sample. Figure 4 shows that among the ten alternative and antioxidant therapies that participants were asked about, vitamin D, vitamin B12, folic acid, zinc, selenium, and CoQ10 were of similar utilization percentages. Thus, expanding the discussion on each one of these therapies will only make the manuscript larger. The author hopes that the reviewer agrees on this reasoning.

3. *Please add error bars to your bar graphs*

**Our response:** The error bars usually refer to the variability of data and indicate how far this data is from the standard, error free, data. The author is afraid that this won’t be applicable to this set of data as it represents a single time answer of Yes/No questions in the conducted survey. The graphs simply represented either the percentages or the actual number of participants who answered certain questions in the survey.