Author’s response to reviews

Title: Overtime trend of thyroid hormones and thyroid autoimmunity and ovarian reserve: A longitudinal population study with a 12-year follow up.

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Response (R) to reviewer comments (C)

We sincerely appreciate the valuable comments of the reviewers on our manuscript entitled: “Overtime trend of thyroid hormones and thyroid autoimmunity and ovarian reserve; a longitudinal population study with a 12-year follow up”. We have provided a revised version based on these comments (C), along with a point-by-point response (R) to each comment and hope that the responses meet your expectations. Please do not hesitate to inform us if any further changes are required.

Yours Sincerely

Fahimeh Ramezani Tehrani, MD
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Reviewer reports:

David Unuane, Ph.D., M.D. (Reviewer 1): This longitudinal observational study with a 12 year follow up aims to observe and compare the overtime evolution of thyroid function parameters and anti-TPO status in fertile women with different ovarian reserve status. Between groups comparison is performed according to different subgroups of ovarian reserve as indicated by age specific quartiles of AMH.

The present manuscript raises some major concerns:

* General remarks:

C1: There are several grammatical errors which makes it difficult to read and comprehend the manuscript especially in the discussion section. This would need some thorough revision.

R: The paper has been edited by native speaker, an academic faculty member of the Research Institute for Endocrine Sciences, IRES.

C2: The discussion section is too long, very often out of scope and lacking structure. There is need for downsizing, concentrating on the major aspects of the manuscript and avoiding repetition.

R: The discussion has been thoroughly with more focus on the main findings.

* Introduction:

C1: Line 57: I would replace thyroid "disease "by thyroid "dysfunction ".

R: Replaced as suggested.

C2: Line 66: I would refrain from using the term "interaction" as it implies some causal relation. I would rather use "any relation". The same comment can be applied for line 220 (discussion).

R: In statistics, interaction occurs when considering the relationship among three or more variables, and describes a situation in which the effect of one variable on an outcome depends on the state of a second variable at different levels of third variable. In our study, the interaction effect of follow-up years × AMH quartile status shows how the effect of AMH quartile status on thyroid functions changed overtime.

Since the replacement the term of “interaction” may change the statistical meaning, we prefer to keep this format, and have added this explanation to the method section of our manuscript.
* Methods:

C1: Were the patients interviewed and examined again at follow up visits or only at the entry of the study?

R: Yes, all participants were re-interviewed and re-examined at each follow up, a point that has been highlighted in the material and method section.

C2: At baseline some of the included patients showed to have some degree of thyroid dysfunction (table 2). Were these patients then excluded from the study as probably some would have needed treatment with levothyroxine or anti-thyroid drug?

R: Yes, we excluded all of participants who received levothyroxine or anti-thyroid drug, a point highlighted in the material and method section and added as footnotes to the tables.

C3: Line: 83: please use levothyroxine instead of thyroxin

R: Thank you; the term has been replaced as suggested.

C4: Line 138: TPO > 35 IU/L/ml was considered as TPO Ab positivity. Is this cut off based on a reference population in Iran (or comparable reference population) were this study was conducted?

R: A valuable comment; yes, we used the cut off value that was identified in Tehran Thyroid Study; related references have been added to the text.

* Discussion:

C1: Line 228: although in the study by Monteleone et al for the first time the presence of thyroid antibodies in ovarian follicular fluid was demonstrated also found a significantly lower oocyte fertilization and percentage of grade A embryos when comparing infertile women undergoing IVF with thyroid autoimmunity to negative controls; however any pathophysiological mechanism is purely speculative. This should be made clear in the manuscript.

R: Thank you; agreed and this has been revised accordingly.

C2: Line 232: The authors state that "A study conducted among infertile women seeking gonadotropin treatment, revealed that TPO Ab positive women, compared to negative ones, have a poorer ovarian response to gonadotropins referring to the study by Monteleone et al. However in this study I cannot find any data on response to gonadotropins."
R: Thank you for your valuable comment. In this study infertile women received treatment protocol as “Controlled ovarian stimulation with 2–6 ampoules/day, according to basal FSH levels and age, of recombinant FSH (Gonal FÔ; Serono, Italy) after a pre-treatment with oral contraceptives. What we meant by “poorer ovarian response to gonadotropins” was the same as what you have mentioned” significantly lower oocyte fertilization and percentage of grade A embryos”; however we have revised to prevent of any misunderstanding.

C3: Line 241: the author’s referred to heterogeneity between studies to explain the controversial results. Could the authors explain as to what exactly is meant by this?

R: We meant some studies were conducted among infertile, while others were conducted on fertile or both fertile and infertile women, which may demonstrate different results. This part has been revised as well.

Lucy Ann Behan (Reviewer 2): This is an interesting and well written analysis of differences in thyroid function and autoimmunity over time based on baseline ovarian reserve in a large cohort reproductive age women with "documented natural fertility" followed up for 12 years.

Many studies in this area focus on infertile women which can result in a skewed perception of the impact of TPO antibodies on ovarian reserve and fertility, whereas this group focused on this occasion on the association between thyroid function, autoimmunity and ovarian reserve.

Findings included

C 1: Higher baseline TPO levels in the women in the lowest ovarian reserve category, although TPO positivity was no different between the AMH quartiles at baseline as per table 2 - I think this should be emphasized more in the manuscript.

R: Yes, as you mentioned, an important point. As our data showed, although the trend was not statistically significant, more frequent positive thyroid antibodies were seen in the lowest AMH quartiles at baseline; this has been emphasized in the discussion section.

C2: Although the odds ratio of TPO positivity was 2.08 fold higher in Q1 compared to Q4, I think the concluding statement of the abstract should be less strong and suggest that the Q1 group MAY be at a higher risk of hypothyroidism overtime.

R: Agreed, this has been revised accordingly.
C3: If the authors are tight on space for tables Table 1 could absorb table 2 and still be very clearly understood

R: Since based on guideline of the journal, the number of tables of the MS is acceptable, so we have kept this format.

C4: Table 4.legend - anti-mullerian hormone missing an "L"

R: Corrected as suggested