Author’s response to reviews

Title: "Hypothyroidism screening during first trimester in pregnancy"

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Author’s response to reviews:

Professor Howard Berger

Editorial Board

BMC Pregnancy and Childbirth

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Dear Professor Howard Berger,

Many thanks for your email of 5th August 2017, concerning revision of our manuscript PRCH-D-17-00502, entitled "Hypothyroidism screening during first trimester in pregnancy".
We have followed the entire editor and reviewers’ suggestions and hope it will now be in accordance with the journal style.

RESPONSE TO EDITOR’S AND REVIEWERS’ COMMENTS:

Editor’s comments:

1. One of the main issues raised was the need to revise the manuscript to reflect the content and recommendations of the 2017 ATA Guidelines for Diagnosis and Management of Thyroid Disease in Pregnancy. This will make the paper relevant at the time of publication and generalizable to the North American population.

Response:

Thank you, following to the editor’s suggestion we have updated the manuscript according to the new 2017 ATA Guidelines Diagnosis and Management of Thyroid Disease in Pregnancy. In fact, we consider that one of the strengths of the article is the applicability of the cut-off proposed by ATA 2017 to our population.

Reviewer 1 comments:

1. Some English grammar and editing is recommend

Response:

A native speaker from BioMed Proofreading® LLC has copyedited the manuscript for improving the language.
2. The aim of the study should be presented in the abstract

Response:

In Methods of the Abstract we have included the aim of the study “The aim of this research was to determine the correct thyroid-stimulating hormone cut-off point for subclinical hypothyroidism screening in the first trimester of gestation in a population of our clinical area”

3. I suggest to strikeout the first paragraph of the results in the abstract, as it seems unnecessary data for the abstract that should be kept to the main manuscript only. Currently this information is not presented in the main manuscript.

Response:

As suggested the unnecessary data have been moved from the abstract, to the main manuscript.

4. The abbreviations os SCH, anti-TPO and anti-TG should be clearly stated, even in the abstract.

Response:

All the abbreviations have been stated in the abstract.

5. "although it is well accepted…". This sentence is too long and confusing.

Response:

Thank you, the sentence has been reviewed.

6. In the meta-analysis by Maraka et al. you failed to mention the association with ruptured membranes.
Response:

As suggested, the outcomes associated with SCH, proposed in the meta-analysis of Maraka et al. have been correctly mentioned.

7. The latest ATA guidelines (Alexander et al. Thyroid 2016) suggest that in the absence of population specific nomograms for TSH the cutoff to define hypothyroidism is 4.0 and not 2.5. It seems that reference 5, 6 do not cite the above mentioned international guideline by the ATA and ES, and that they are outdated.

Response:

We have followed these suggestions in response to Editor’s comment.

8. Refrain from using "patients", as the participants are per definition healthy pregnant women.

Response:

We agree with the reviewer, and have changed from patients to participants.

9. It seems that the first paragraph is misplaced, as it is a repetition of the study's objective, which should, and indeed does, appear in the introduction.

Response:

We have followed this suggestion.

10. Many details are missing from the methods section, which currently seems to be too concise. The following matters should be addressed: 1) how was clinical data obtained - charts, files, interview, questionnaires; 2) What was the indication to visit the participating clinics - routine
pregnancy follow up; 3) was other data considered. Such as parity, prior and current pregnancy complications (and if so, this data should be clearly defined and presented in the results)

Response:

As suggested, we have included this data in the methods.

“Information about maternal age, initial weight and height, parity, prior or current pregnancy complications and BMI was collected by interview and exploration, during the first trimester routine visit”.

11. Please explain how the sample size was established to be 100 patients? What is the "previous sample"? And what is a resample by the bootstrap technique?

Response:

To estimate sample bias, standard errors, and 95% confidence intervals, smoothed centile curves were fitted to 5,000 nonparametric bootstrap replicates drawn from the initial sample of 100 participants. The 95% confidence intervals are the standard intervals of Efron and Tibshirani.

12. The section that starts with: "to establish the cut-off…” belongs in a separate paragraph detailing the data analysis methodology. It is not part of the statistical analysis.

Response:

We have changed this section to the Methods part.

13. It also seems important that data on prior medical history, that may be relevant to the thyroid function, be at collected and considered. For example, prior abortions, prior preterm deliveries, family history of thyroid disease etc. - all these may be confounders. As this is an attempt to establish a nomogram, the population of the study should be as "clean" as possible from potential cofounders.
Response:

As suggested we have added this information.

14. Table 1 and the reference values for the kits is not part of the results, and are more appropriate as part of the methods.
Response:
We have changed the reference of Table 1 to the Methods part.

15. Vital results are missing - Weigh, Height, BMI, age
Response:
Results about weight, height and BMI have been included in the Results.

16. The quoted ATA guidelines are outdated. The authors should address the newer guidelines from 2016.
Response:
We have followed these suggestions in response to Editor’s comment.

17. I fail to see the relevance of table 4. It is not part of the study, which aims to be an original article not a textbook chapter or review.
Response:
As suggested, Table 4, and references to it, has been eliminated from the manuscript.
18. Please offer strengths and limitations of the study.

Response:

The inclusion in our study of pregnant women with TPO antibodies within the group classified as SCH is a limitation. However, at present, the determination of TPO antibodies is not included in our screening strategy.

We consider that one of the strengths of the article is the applicability of the cut-off proposed by ATA 2017 to our population.

19. References 8 and 9 are missing.

Response:

References 8 and 9 are referred in the Discussion after the phrase “has already been reported by other studies conducted outside the United States (8, 9).”


20. Editions and page numbers are missing for references 11, 12.

Response:

Edition in references 11 and 12 has been done.

Reviewer 2 comments:

1. In the abstract the age range was 16.27 - 32.13 but the mean age was 32.13 so 32.13 cannot be the upper limit of the range AND the mean.

Response:

Of course this was an error, we have corrected it. The mean age of the pregnant women included was 32.13 ± 5.21 years (range 16.27 – 46, 23).

2. Reference #9 typo - autoimmunity instead of autoimmunity

Response:

As suggested, this has been changed.

3. Overall an interesting study but likely written before the 2017 ATA Guidelines for Diagnosis and Management of Thyroid Disease in Pregnancy. In these Guidelines, there are suggestions on how to determine population specific reference ranges: Recommendation #1 - Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPO Ab status.

Response:

Obviously, this represents a limitation to the study. Since our research was conducted prior to the publication of the 2017 ATA Guidelines Diagnosis and Management of Thyroid Disease in Pregnancy, pregnant women with anti-TPO positive were not excluded from the study. However, as we stated in the conclusions, further studies are needed to demonstrate whether screening only in pregnant women at risk, including the determination of anti-TPO, would be more cost-effective.

4. The premise of this article is looking at the incidence of SCH using a TSH cut off above 2.5 vs. above their 97.5th percentile. But a 2.5 mIU/L TSH cutoff is no longer being advocated - therefore the manuscript should be reworked as another population based reference range (see
Table 4. Reference Ranges for Thyrotropin and Free Thyroxine During Early Pregnancy Worldwide) rather than comparing the incidence of SCH with 2.5 vs. their 97.5%ile of 4.7

Response:

Although in the USA the cutoff point has already been updated (ATA 2017) in Spain, this has not been assumed yet by the Spanish Society of Gynecology and Obstetrics (SEGO). Therefore, it seems pertinent to include the observed difference in the incidence of SCH using both cut-off points as a way of supporting the recommendations of the 2017 ATA Guidelines Diagnosis and Management of Thyroid Disease in Pregnancy in our country. As a complement to the above, we determined the incidence found using the three cutoff points 2.5 mIU/ml, 4 mIU/ml and 4.7 mIU/ml.

5. As well, the Guidelines recommend that the reference range should only include women with NEGATIVE TPOAb status so these should be excluded from the analysis.

Response:

This represents a limitation to the present study. Since our research was conducted prior to the publication of the 2017 ATA Guidelines Diagnosis and Management of Thyroid Disease in Pregnancy, pregnant women with anti-TPO positive were not excluded from the study. As we stated in the conclusions, further studies are needed to demonstrate whether screening only in pregnant women at risk and including the determination of anti-TPO, would be more cost-effective.

6. The results should include the patient characteristics (only included in the abstract not in the body of the article) and should include parity and other characteristics if known (ideally including iodine status or at least indicating if this area is an iodine deficient or sufficient area based on studies).

Response:

We have already added this information in the results part, all the participants belong to an iodine sufficient area, based on the literature.

7. In light of V. THYROID AUTO-ANTIBODIES AND PREGNANCY COMPLICATIONS of the Guidelines, the discussion on TPOAb is too cursory - almost an afterthought in the last paragraphs of the discussion. The conclusion that TSH levels were not able to predict TPOAb
status are interesting but do not warrant the conclusion to consider screening all women for TPOAb, especially since there is no evidence outside of RPL that treatment is of any benefit.

Response:

Thank you, we have adapted the conclusions of our manuscript. Indeed, from our results it is not possible to conclude that it is necessary a screening for TPO Ab of all pregnant women.

However, we suggest that further studies would be necessary to clarify whether restricting screening exclusively to pregnant women at risk, and if including the determination of anti-TPO would be more cost-effective.

8. Overall, this is an interesting population based study that with the above modifications and rewritten to reflect the 2017 guidelines would be of interest in helping other populations develop their Pregnancy Specific Reference Range.

Response:

Thank you.

Editorial Policies:

Where a mandatory Declarations section is not relevant to your study design or article type, please write "Not applicable" in these sections.

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must confirm this under this sub-heading and also provide their reasons.

Response:

Declarations have been ordered according to the journal style.