Author’s response to reviews

Title: Association between thyroid-stimulating hormone and maternal hemodynamics in hypertensive disorders of pregnancy: An observational study

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Author’s response to reviews:

Dear editor,

This was a revision for manuscript PRCH-D-19-00859. Thank you very much for your comments and further instructions. We also appreciated the careful work of the reviewers and their constructive comments. We have carefully studied the comments and made corrections accordingly, which were highlighted in bold and blue color in the revised version of the manuscript. In addition, the language has been edited by the website recommended by your journal. The detailed responses are listed. We would like to re-submit this revised manuscript, and wish it is acceptable for publication in your journal.

Looking forward to hearing from you.

Best regards,

Zhengfeng Xu
The detailed responses to the editor’s and reviewers’ comments:

First of all, we thank the editor and the reviewers for their careful review and the positive and constructive comments and suggestions. The point-to-point response to the comments were listed below.

Editor comments

1. Table legends need to clearly define what summary statistics are shown.
Response:

   Thank you for your advice. We have changed the table legends of Table 4 into ‘Association between thyroid function indicators and reduced CO’, which was more clearly defined the summary of the table.

2. All continuous data in table 1 appear to be presented using parametric summary statistics, however there is no information on whether data were normally distributed.
Response:

   We are sorry for the misunderstanding of table 1. Urea nitrogen, creatinine, GFR and albumin levels were normally distributed. BMI, birth weight and gestational ages were also normally distributed. They were expressed as mean± standard deviation.

3. Median (25th percentile, 75th percentile) is preferable to median (minimum, maximum), as the range is dependent on sample size.
Response:

   Thank you very much for your advice. All the skewed distributed data were expressed as median (25th percentile,75th percentile) accordingly. We are appreciated for the advice and the data expressed were more reliable.

4. Table 3 includes a large number of correlations, a few of which will be significant by chance. There is no information on whether the authors adjusted for multiple comparisons. Please provide 95% confidence intervals for r values, and focus on effect sizes rather than significant p-values.
Response:

   Thank you very much for your careful and precise review. The revised Table 3 was adjusted for multiple comparisons. We used Bonferroni’s correction for multiple correlations adjustment and the corrected p-value was 0.0025. After adjustment, only CO had significant correlation (p<0.0025) with TSH level. The multiple correction description was added in the table legend and method section of the manuscript. The 95% confidence intervals for r values in Pearson correlation tests were added in Table 3.
5. The statistical analysis section refers to t-tests, non-parametric tests, Chi-squared tests, and Fishers exact tests, however it is unclear where in the manuscript these tests were used.

Response:

We are sorry for the mistake. T-tests, non-parametric tests, Chi squared test and Fishers exact tests were not used in the manuscript and the descriptions were deleted. In the factor selection process in regression analysis for CO reduction, t-tests and Chi-square tests were used to compare the differences of normally distributed continuous baseline data and categorical data, respectively. These were added in supplementary Table 1. Specific tests descriptions were added in the corresponding table legends.

6. Please specify exactly what statistical tests were used in the table legends. Avoid non-specific terms (i.e. non-parametric tests). Greater detail is needed regarding multivariate models and logistic regression; how factors were selected, etc.

Response:

Thank you very much for your careful review and the valuable suggestions. Specific statistical tests were added in corresponding table legends. In Table 1 and 2, there were no statistical tests. In Table 3, Pearson correlation test was used and was described in table legend. Bonferroni’s corrections for multiple correlations were used and described in table legend. In Table 4, univariate and multivariate logistic regression analysis were used. In supplementary Table 1, continuous variables which were all normally distributed were compared by t-tests. Categorical variables were compared by Chi-square test.

We compared the baseline characteristics of normal CO and reduced CO groups. This information was added in supplementary Table 1. Factors have a statistical significance between two groups were considered as confounding factors and were pooled into univariate regression analysis. Factors with a p-value less than 0.05 in univariate analysis were pooled into multivariate regression analysis.

In the Patients and Methods section of the manuscript, we excluded patients with previous thyroid disorders and patients took thyroid substitution medications before hemodynamic exams. Besides, patients with previous cardiac, chronic hypertensive disorders were excluded. All these criteria were mentioned in the manuscript. Patients took anti-hypertensive medications during pregnancy before hemodynamic exams were also excluded. This exclusion criterion was omitted in the previous version of the manuscript and was supplemented in the Patients Section in the revised manuscript. We are very sorry for the omission of this description.
7. Please limit abbreviations to a few essential terms – there are too many for a reader who is not intimately familiar with the field to keep track of.

Response:

We apologize for the lack of brevity in the article and we have deleted some of the abbreviations. Only important abbreviations used in multiple places in the article were left.

8. As was highlighted by both reviewers, it is important not to infer causation from this small, correlative study.

Response:

We are sorry for this mistake and we appreciated this important and constructive advice. We have corrected all the causation descriptions into correlation descriptions throughout the manuscript.


Response:

Thank you for your instructions. We have studied the website and the RRIDs. The research resource identifiers of RRIDs were added for SPSS, MedCalc and assays for thyroid hormones in the manuscript.

Reviewers’ comments

Reviewer 1

This is a study looking at the correlation between TSH and free T4 with maternal hemodynamics in women with gestational hypertension. It is a cross-sectional study and thus any conclusions on cause and effect need to be very cautious. There is no comparison to women without gestational hypertension, which I think is a limitation, as it is hard to know if the correlation between TSH and CO really has anything to do with gestational hypertension, or whether this is true of all pregnancy.

Response:

We appreciated your valuable comments and suggestions. We have corrected all the causation descriptions into correlation descriptions in this manuscript. There was no comparison to women without gestational hypertension and it was indeed a limitation of this manuscript. We have added this into the limitation section of the manuscript. The conclusions of the study were only restricted to pregnant women with GHD during the third trimester. It was unclear from this study that whether this association also existed in normotensive pregnancies. These were all added into the limitation section of the manuscript and warrant future study.
1. The authors do not say how many women had gestational hypertension versus preeclampsia. It would be useful to know what type of hypertensive disorders the women in this study had, as preeclampsia is characterized by more systemic endothelial dysfunction that gestational hypertension alone. One would expect more hemodynamic alterations in the more severely affected group and it would be good to see this added to any models (preeclampsia vs. gestational hypertension).

Response:

We appreciated very much for your comments and suggestions. The exact numbers of women had gestational hypertension versus preeclampsia were added into Table 1 and Supplementary Table 1. It was true that the ratio of patients with reduced CO in PE group was significantly higher than that in gestational hypertension group by Chi-square test. However, whether a pregnant woman was complicated with gestational hypertension or preeclampsia was not significant in univariate regression analysis for reduced CO (Table 4). This may due to the fact that the PE patients in our hospital are within a mild stage and patients with severe PE stage in our hospital were few.

2. Were urinary proteins measured? Women with preeclampsia and heavy proteinuria could lose thyroid-binding globulin in the urine and develop subclinical hypothyroidism.

Response:

We are sorry for the lack of clarity of the details of the baseline description. 24 hours of urinary proteins of the enrollment patients were measured and the results were added in Table 1 and Supplementary Table 1. The levels of urinary protein were not significantly different between normal CO and reduced CO groups, indicating that urinary protein may not be a confounding factor regarding the relationship between TSH and CO.

3. Why would cardiac output, but not cardiac index, but correlated with TSH?

Response:

Thank you for your careful review. Cardiac output is the result of direct determination by ICG instrument. However, cardiac index was adjusted for the body surface area. The normal range of CI in the specification takes into account both the normal range of CO and the normal range of body surface area of Chinese population. Body surface area may be a confounding factor. Unfortunately, the body surface area values were not directly output from ICG instruments. In order not to be misleading, we removed indicators involving body surface area, such as cardiac index, stroke volume index and systemic vascular resistance index from the manuscript and tables in the revised version.

4. On page 9, line 193, would not say that TSH contributes to cardiac output reduction as you have only identified a correlation, not a causation. Similarly, the first line of the discussion uses the word 'risk'. This study has only looked at associations and a cross-sectional study cannot assess risk.
Response:

We are sorry for this mistake. The expression of ‘elevated TSH level contributed to cardiac output reduction’ was corrected into ‘elevated TSH level was associated with reduced cardiac output’. The expression of ‘risk’ in the discussion was also corrected into ‘association’.

5. The authors appropriately bring up the associations of thyroid disorders and growth restriction, but do not provide any data in this regard. What were the birth weights, number of low birth weight infants, etc.? Did women with low cardiac output have fetal growth restriction as hypothesized?

Response:

We really appreciated for your careful review and your suggestions. The values of birth weight and the number of low birth weight infants were added in Table 1. Birth weight of the overall enrollment patients was 2862.07±787.48g, and a total of 49 infants were below 2500g of birth weight (Table 1). The birth weight of GHD patients with normal TSH level and elevated TSH level was 3037±673g and 2635±867g, respectively (p=0.002). This was added into Results Section of the manuscript. The result indicated that thyroid disorders may be associated with growth restriction. The birth weight of GHD women with normal CO and reduced CO were 2890±774 vs. 2250±510g, p=0.002. The number of infants with low birth weight was also significantly different between normal CO and reduced CO groups (p=0.013, Supplementary Table 1). This indicated that women with low cardiac output may associated with fetal growth restriction.

6. It would nice to see if this relationship between CO and TSH is true regardless of whether a woman has hypertensive pregnancy. Are there studies looking at maternal hemodynamics in relation to TSH in normal pregnancy? This would be a good control group for this study.

Response:

Thank you for your advice. There was a study demonstrated that decreased TSH level was associated with increased CO and the risk of pulmonary hypertension in general females (not pregnant women) [1]. We are sorry to say that there was no relevant literature on this relationship in normotensive pregnant women. This was the first research to our knowledge revealed the relation of maternal hemodynamics with TSH in pregnancy. Lacking the control group was a limitation of our study. We only revealed the relation between CO and TSH in GHD women in our study. The fact that lacking normotensive pregnant women as a control group makes it impossible for our study to determine whether this relation exists alone in GHD or all pregnant women. This was added in the limitation section of the manuscript. We will optimize future research to further explore this issue.


7. Page 12, line 261. Cannot say that you discovered that elevated TSH contributes to CO reduction in GHD without comparing to women without GHD.
Response:

We are sorry for this mistake. We have corrected this causal expression into association expression.

8. In Table 1, the number of women with gestational diabetes seems quite high. How was this defined and is this typical of this population?

Response:

We are sorry for this misunderstanding. The diagnosis criterion of gestational diabetes was positive OGTT test at 24-28 weeks of gestation. The incidence of gestational diabetes in our hospital in recent years was approximately 20%-25%. The incidence of gestational diabetes in our enrolled population was 21.5%. This high incidence of diabetes was not typical of this population, and the distributions of the number of diabetes patients were not significant between normal and reduced CO groups. This information may serve as a confounding factor for misunderstanding and we deleted this information from the revised version of the manuscript.

9. Would include urine protein and birthweights in Table 1 as well. What gestational age did women go on to deliver at?

Response:

Thank you for your reminders and suggestions. We have added the information of urine protein, birthweight and gestational age at delivery in Table 1.

10. Table 2 - explanations of the abbreviations are needed below the table.

Response:

Thank you for your advice. We have limited the abbreviations to a few essential terms as the editor advised. The table contains the full names of most hemodynamic indicators. As for the essential indicators including CO and SVR, the explanations of these abbreviations were added below the table.

11. Table 3 - I would suggest that authors reorganize Table 3 with the r and p values side by side, instead of on top of each other.

Response:

We apologize for the wrong format of Table 3. We have reorganized Table 3 and the r and p values were side by side.

12. Would avoid CO disturbance and instead so reduced cardiac output, or something to that effect.

Response:

Thank you for your instructions. We have avoided the expression of CO disturbance and were corrected into CO reduction or reduced CO.
13. Some grammatical and English errors need to be corrected.

Response:

Thank you for your valuable comments and advice. The language of the manuscript had been edited by the Springer Nature Language Editing Service as the journal recommended.

Reviewer 2

This is an interesting study, adding to current knowledge on maternal hemodynamics in pregnancies complicated with hypertension (GHD). The authors report an association between thyroid dysfunction and GHD, similar to what has been reported for cardiac and vascular diseases. Today it is not yet clear whether the latter association is causative or simply co-existing as two symptoms of the same underlying pathology.

Response:

Thank you very much for your constructive and positive comments to the manuscript. This study revealed the association between thyroid function with maternal hemodynamics in GHD during the third trimester. The conclusion should be limited to an association relationship instead of a causative relationship.

1. The authors' conclusions on a causative link between thyroid dysfunction and GHD go too far in the current version: throughout the paper they state that thyroid dysfunction INDUCE, LEAD TO, PREDISPOSE TO hemodynamic dysfunctions. The paper's message will be scientifically stronger when they should interpret thyroid and maternal hemodynamic dysfunctions to two co-existing co-morbidities.

Response:

We appreciated very much for your comments and suggestions. We feel sorry for the mistake. All of the causative relation descriptions in the manuscript have been corrected into co-existing or association descriptions.

2. Hemodynamic changes during pregnancy are different between gestational trimesters. The authors have studied cases in the third trimester, so the observed associations are to be limited to this trimester only. An example: in the third trimester, cardiac output is known not to rise anymore (line 224-228), etc…

Response:

Thank you very much for your advice. The patients enrolled in the present study were during the third trimester. The conclusion of the observed association between TSH and CO was limited to the third trimester. The corresponding sections of the manuscript were added with the description that the conclusions were limited to the third trimester. Lacking longitudinal studies on the changes of TSH and CO was a limitation of the present study. This was also added in the limitation section of the manuscript.
3. Current tables are too abundant, however they can function very well as supplementary material. Tables embedded in the text should be much more condensed and focused.

Response:

We are sorry for the abundancy of the tables and appreciated very much for your advice. The indirect hemodynamic parameters were deleted from the current tables. Only parameters have essential clinical significance were left. Only baseline characteristics and baseline hemodynamics, correlation analysis tables were left in the manuscript. As logistic regression indicator selection process description, comparison of patients’ baseline characteristics between different CO groups was added as Supplementary Table 1.

4. The Discussion section also is much too expanded and unfocussed. The authors could limit this section to the reported associations of thyroid dysfunction with other cardiovascular diseases, endothelial function/dysfunction and the hormonal environment of pregnancy (HCG).

Response:

We appreciated very much for your valuable suggestions. We have corrected the discussion section accordingly. The discussion section of the manuscript should be more condensed and focused than before. The first paragraph was focused on the adverse perinatal prognosis of elevated TSH. The second paragraph of the discussion section was focused on the reported associations of thyroid dysfunction with cardiovascular disorders, endothelial dysfunction. The third paragraph was focused on the hemodynamic alteration during pregnancy and the potential linkage of TSH and CO. The fourth paragraph mainly focused on the limitation of the research. The last paragraph was the conclusion.

5. Language can do better.

Response:

Thank you for your valuable comments and advice. The language of the manuscript had been edited by the Springer Nature Language Editing Service the journal website recommended.