Author’s response to reviews

Title: Association between thyroid dysfunction and perinatal outcomes in women with gestational hypertension: a retrospective study

Authors:
Juan Gui (514325204@qq.com)
Wangming Xu (tjobg2012@163.com)
Jie Zhang (2662458105@qq.com)

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Author's response to reviews:

Re: submission of our revised manuscript (PRCH-D-19-00132R1) to BMC Pregnancy and Childbirth “Association between thyroid dysfunction and perinatal outcomes in women with gestational hypertension: a retrospective study”

January 23, 2020

Dear Editor,

Dear Reviewers,

We would like to thank you for your review and comments regarding our submitted manuscript entitled “Association between thyroid dysfunction and perinatal outcomes in women with gestational hypertension: a retrospective study”. Enclosed please find the revision of our manuscript. The authors are Wangming Xu, Jie Zhang and me.

We appreciate the comments of the two reviewers and the Section Editor and have incorporated their suggestions in the revised manuscript. We have invited Dr. Rui-Hao Wang (from Department of Neurology, University of Erlangen-Nuremberg, Germany) to improve the quality of written English. All changes are highlighted in grey.

We believe that the comments significantly improved the manuscript and hope that the manuscript might be suitable for publication in the BMC Pregnancy and Childbirth.

Below, please find our responses to the reviewers and to the Section Editor. Thank you for your attention!
Sincerely,

Dr. Juan Gui

Re: submission of our revised manuscript (PRCH-D-19-00132R1) to BMC Pregnancy and Childbirth “Association between thyroid dysfunction and perinatal outcomes in women with gestational hypertension: a retrospective study”

Responses to Reviewer #1

Response to comment #1

Abstract

* Please add the short background at the beginning of the abstract.

We thank the reviewer for the suggestion. In the revised manuscript, we have now added the short background at the beginning of the abstract (page 2 line 2-3 “Previous studies showed that thyroid dysfunction in women with gestational hypertension could negatively affect maternal and fetal outcomes.”).

* Please present the OR and 95%CI in all association results.

We have presented the OR and 95%CI in all association results (page 2 line 21-22, page 3 line 1-7 “After adjustment, both severity of gestational hypertension (OR=4.360, 95%CI [2.050, 9.271], P<0.001) and thyroid dysfunction (OR=3.011, 95%CI [1.248, 7.262], P=0.014) were associated with higher risk of preterm birth, while the onset time of preeclampsia (OR=0.031, 95%CI [0.009, 0.110], P<0.001) was negatively associated with the risk of preterm birth. Similarly, both severity of gestational hypertension (OR=4.023, 95%CI [1.933, 8.372], P<0.001) and hypothyroidism (OR=11.306, 95%CI [1.040, 122.889], P=0.046) were significantly associated with higher risk of low birth weight, while the onset time of preeclampsia (OR=0.097, 95%CI [0.033, 0.282], P<0.001) was negatively associated with lower risk of low birth weight.”).

* Please specify in the method part, the type of study.

This was a retrospective case-control study and we have added in the method part (page 2 line 6).
Response to comment #2

Introduction

It is recommended to express the incidence of hypothyroidism during pregnancy.

We appreciate the reviewer’s comment and have now incorporated the incidence of hypothyroidism during pregnancy in the introduction (page 4 line 9-15 “Thyroid dysfunction is common among pregnant women. According to previous reports, the prevalence of clinical overt hyperthyroidism or subclinical hyperthyroidism is about 0.1%-0.4% during pregnancy. The prevalence of hypothyroidism is about 2.5%, with clinical hypothyroidism accounting for 0.2-0.3%, and subclinical hypothyroidism for 2%-3%, while hypothyroxinemia for 1%-2%. According to domestic reports in China, the prevalence of gestational clinical hypothyroidism is approximately 0.5-0.6%, with subclinical hypothyroidism 2%-3%, and hypothyroxinemia 1.6%. The prevalence of subclinical hypothyroidism is the highest.”).

Response to comment #3

Method

* How was the information collected? Were the hospital records used?

We thank the reviewer for the questions. We collected the data from Electronic medical records of Renmin Hospital of Wuhan University. We have added this information in the method (page 6 line 6-10).

* The method section seems to be incomplete and there is no clear explanation for the method of data collection. It is also necessary to explain how to collect information about thyroid hormone tests. Do all of these tests were conducted in a laboratory? Please explain more about the method of collecting information.

We thank the reviewer for the comments. In the revised manuscript, we have now added the inclusion criteria (page 6 line 13-17), exclusion criteria (page 6 line 17-22). Thyroid hormone tests were completed by the laboratory department of the hospital. Serum TSH, FT4, FT3 and TPOAb levels were measured using electrochemi-luminescence immunoassay (Cobas Elesys 601, Roche Diagnostics).

* In Statistical analysis section, how we can confirm the sample size? Please give some information about it.

We have used the online formula to calculate the sample size (https://www.stat.ubc.ca/~rollin/stats/ssize/caco.html). The total sample size is about 104 patients.
* It is necessary to define the terms of "hypothyroidism" based on TSH levels in this study.

In the revised manuscript, we have given the definitions of various types of thyroid dysfunction such as hypothyroidism, subclinical hypothyroidism, hypothyroxemia, gestational thyrotoxicosis, hashimoto thyroiditis according to ATA 2017 guideline. (page 7 line 12-22, page 8 line 1-2)

* Perinatal outcomes must be defined and it should be determined which of the outcomes are being studied in this study.

Two perinatal outcomes, preterm birth and low birth weight were analyzed in this study and the definitions were given in the method part. (page 7 line 10-11)

* It is recommended to use a flowchart to illustrate the study groups.

We use a flowchart to illustrate the study groups (page 6 line 22).

Response to comment #4

Results

* In the last sentence of results section "FT3, rate of hypothyroidism and rate of low T3 and low T4 were associated with at least one adverse outcome (P<0.05)". This sentence does not look clear and needs to be edited. What is the relationship between FT3 and adverse outcome?

We have deleted those confused sentences in the result section. We discussed the relationship between thyroid dysfunction and adverse fetal outcomes in the discussion part. In this study, we could find only two types of thyroid dysfunction associated with low neonatal birth weight, hypothyroidism and FT3 and FT4 both below the normal lower limit. (page 13 line 11-14)

* Please use the full name of FT3 and FT4 and then abbreviation when it firstly appears in the text.

In the revised manuscript, we have now given the full name of FT3 and FT4 when it first appeared. (page 7 line 15-16 “serum free thyroxine (FT4)”, page 8 line 3 “free triiodothyronine (FT3)"

* What is the meaning of "FT3 and FT4 decreased" in this study? Has a certain amount of hormonal loss been considered?

We are sorry for these confused words. We have changed the description as “FT3 and FT4 both below the normal lower limit”.

* It is suggested to compare the outcomes of the groups in a separate table.
We have revised the format of Table 3. The new table might be more clear.

* In tables 1 and 2, please report all p-values.

We have added all p-values in table 1 and 2.

* In the subtitles of tables 1 and 2, in order to clarify the results, it is suggested that Instead of sentence "a Significantly different with the pregnant induced hypertension_ b significantly different with the late onset preeclampsia", insert the following sentence: a Early onset preeclampsia vs the pregnant induced hypertension _ b Early onset preeclampsia vs late onset preeclampsia.

We are appreciated for the suggestion. We have added all p-values for the comparison of every two groups in table 1 and 2.

* In Tables 1 and 2, specify the values given for each of the variables are mean (SD) or n (%)

We specified all the values in the table 1 and 2.

* Please mention the Reference Group in Table 3 for each Characteristics.

We have added the reference groups after the items. The relationships between severity of gestational hypertension and the neonatal outcomes were performed among PIH, MPE and SPE groups. The relationships between onset time of gestational hypertension and the neonatal outcomes were performed among EPE and LPE groups. The relationship between thyroid dysfunction and the neonatal outcomes were performed among all patients.

* It seems that univariate logistic regression was applied to estimate the association between preterm and low birth with characteristics factors and crude ORs were presented while these relationships could be confounded through variables such as maternal age and so on. I suggest author to run multiple logistic regression and estimate adjusted ORs via appropriate confounding variables as well.

We thank the reviewer for the comment. Associations of thyroid dysfunction, gestational hypertension disease, and neonatal outcomes were assessed by logistic regression, unadjusted first, and then adjusted for age, gestational history, menstrual cycle, family history, history of gestational hypertension. (page 9 line 1-5)

Response to comment #5

Discussion

* The first paragraph of the discussion section is not clear and needs to be edited.
In the revised manuscript, we have now reedited the first paragraph of the discussion section. (page 12 line 2-8 “In this retrospective case-control study, we found that patients with severe preeclampsia, early onset preeclampsia or thyroid dysfunction had higher risk of adverse maternal and fetal outcomes such as preterm birth and low neonatal birth weight. Our data show that the rates of preterm birth and thyroid dysfunction were the highest in the patients with EPE. Although we could not find significant differences between EPE and PIH groups in the rates of thyroid dysfunction (71.9% vs. 56.7%), giving more emphasis on the thyroid hormones in those patients with EPE might reduce some adverse maternal and fetal outcomes.”)

* Please present some underlying pathophysiology associated with findings.

We have added some underlying pathophysiology associated with findings. (Page 12 line 19-21 “Hypothyroidism has been shown to have various vascular pathogenic effects, including endothelial cell dysfunction which is also a pathophysiological basis of gestational hypertension.”)

* In the discussion, the relationship between the findings of the present study and the findings of other relevant research in the world (with references to sources) should be compared and logically analyzed. Were there any study about the effect of thyroid dysfunction on the perinatal outcomes in women with gestational hypertension?

We have analyzed other relevant researches in the discussion part (page 12 line 21-22, page 13 line 1-11, “A study including 16364 singleton births hypothyroid mothers in Finland found that maternal hypothyroidism was associated with higher risks of gestational hypertension (OR=1.20, 95%CI [1.10-1.30]), severe preeclampsia (OR=1.38, 95%CI [1.15-1.65]), preterm births (OR=1.25, 95%CI [1.16-1.34]), major congenital anomalies (OR=1.14, 95%CI [1.06-1.22]), and neonatal intensive care unit admission (OR=1.23, 95%CI [1.17-1.29]). Surks et al showed that increased maternal serum TSH (higher than 10 mIU/L) was associated with increased risk of stillbirth. A study including 25756 women conducted by Casey and colleagues revealed that subclinical hypothyroidism in pregnancies was associated with a 3-fold increased risk of placental abruption (relative risk 3.0, 95% CI[1.1–8.2]). The risk of preterm birth was almost 2-fold higher in women with subclinical hypothyroidism than in those without (relative risk, 1.8, 95% CI[1.1–2.9]). Another study showed that the incidence of premature birth, low birth weight and neonatal asphyxia was significantly higher in pregnant women with hyperthyroidism than that in normal pregnant women.”; page 13 line 20-22, page 14 line 1-9 “A study including 6031 mothers showed that after normalization of the thyroid hormones with appropriate treatment in women developing hypothyroidism in the first trimester, there was no significant difference in the risk of developing preeclampsia compared with the normal pregnant women. However, if the women developed hypothyroidism in the third trimester, they still had a 2.18-fold higher risk of developing preeclampsia. A prospective study in China including 3398 pregnant women found that isolated maternal hypothyroxinemia (IMH) in the first trimester did not increase the risk of adverse outcomes irrespective of whether women received L-thyroxine treatment or not.
However, IMH identified in the second trimester was associated with a significantly increased risk of adverse pregnancy outcomes. The results suggest that thyroid function follow-up during the second trimester is necessary, even if thyroid function is normal during the first trimester.”

* What are the strengths of the study?

Many studies focused only on the first trimester, and did not include all subtypes of gestational hypertension disease. The present study investigated thyroid hormones of women with gestational hypertension disease in the second half trimester and compared various types of preeclampsia according to the severity and the gestational age. Our data show that the incidences of preterm birth and thyroid dysfunction were the highest in the patients with EPE. Comprehensive monitoring thyroid hormones throughout the whole pregnancy and early treatment are very important to reduce the incidence of preterm birth and low birth weight.

* What further studies are recommended in this area?

Due to the retrospective design and the small size of our study, currently we cannot determine whether thyroid dysfunction in the first half trimester or in the second half trimester have a greater effect on maternal and fetal pregnancy outcomes. Data are also lacking regarding whether the treatment is obligatory for patients with FT3 and FT4 both under the lower limit but normal TSH to prevent adverse neonatal outcomes. Certainly, further studies are needed to widen our understanding on thyroid dysfunction and neonatal outcomes.

Responses to Reviewer #2

Response to comment #1

Please state in the Methods if enrolled women with gestational hypertension/preeclampsia were consecutive or not.

We thank the reviewer for the comment. The patients were consecutively enrolled.

Response to comment #2

At what time in pregnancy or after pregnancy where thyroid function tests performed?

We thank the reviewer for the comment. The thyroid function was tested in the second half trimester during hospitalization and completed by the laboratory department of the hospital. Serum TSH, FT4, FT3 and TPOAb levels were measured using electrochemi-luminescence immunoassay (Cobas Elesys 601, Roche Diagnostics).