Author’s response to reviews

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

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Author's response to reviews:

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

November 23, 2019

Dear Editor,

Dear Reviewers,

We would like to thank you for your review and comments 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. All changes are highlighted in yellow.

We believe that the comments significantly improved the manuscript and hope that the article is now acceptable 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-19-00132) 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.

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

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

We thank the reviewer for the suggestion. In the revised manuscript, we have now added the short background at the beginning of the abstract, presented the OR and 95%CI in all association results and specified the type of study in the method part.

Background: Studies had shown that thyroid diseases in patients with gestational hypertension could severely affect maternal and fetal outcomes. This study was aimed to explore thyroid hormones in the second half trimester of pregnancy in different classification of preeclampsia and correlate them with neonatal outcomes of pregnancy.

Methods: We performed a retrospective case-control study and collected data from 135 singleton pregnant women with gestational hypertension or preeclampsia and their offspring who delivered in our hospital from January 2015 to June 2017. The comparisons were among pregnant induced hypertension (PIH), mild preeclampsia (MPE) and severe preeclampsia (SPE) or among PIH, early onset preeclampsia (EPE) and late onset preeclampsia. Maternal basic characteristics, thyroid hormones, and the incidences of adverse maternal and neonatal outcomes were collected from Electronic Medical Records. Logistic regression was used to estimate the associations of thyroid dysfunction and neonatal outcomes in these patients.
Results: SPE and EPE had significantly lower gestational week and neonatal birth weight, and significantly higher incidence of preterm birth than PIH (P<0.001). SPE group had a higher rate of thyroid dysfunction than MPE (P=0.01). Patients with thyroid dysfunction had more incidence of preterm birth and low birth weight than those without (49.3% vs. 25%, P=0.008; 45.1% vs. 27.1%, P=0.047). After adjusted, preterm birth rate was positively associated with the 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), and negatively associated with the onset time of preeclampsia (OR=0.031, 95%CI [0.009, 0.110], P<0.001). The rate of low birth weight was positively associated with the 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), and negatively associated with the onset time of preeclampsia (OR=0.097, 95%CI [0.033, 0.282], P<0.001).

Conclusion: Severe and early onset preeclampsia have more incidence of preterm birth and low neonatal birth weight. Patients with thyroid dysfunction are more prone to preterm birth. Therefore, monitoring thyroid hormones in women with preeclampsia might help us to predict adverse neonatal outcomes.

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.

Thyroid dysfunction is common in pregnant women. According to foreign reports, the proportion of hyperthyroidism and subclinical hyperthyroidism is about 0.1%-0.4% during pregnancy. The incidence of hypothyroidism is about 2.5%, with clinical hypothyroidism accounting for 0.2-0.3%, subclinical hypothyroidism for 2%-3%, hypothyroxinemia for 1%-2%. According to domestic reports, the incidence of gestational clinical hypothyroidism is 0.5-0.6%, subclinical hypothyroidism is 2%-3%, and hypothyroxinemia is 1.6%, among which the incidence of subclinical hypothyroidism is the highest.

Response to comment #3

Method

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

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

* It is necessary to define the terms of “hypothyroidism” based on TSH levels in this study.

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

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

We thank the reviewer for the suggestion. We collected the data from Electronic medical records of Renmin Hospital of Wuhan University. 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 the revised manuscript, we have now added the inclusion criteria, exclusion criteria and given the definitions of various types of thyroid dysfunction such as hypothyroidism, subclinical hypothyroidism, hypothyroxemia, gestational thyrotoxicosis, hashimoto thyroiditis according to ATA 2017 guideline. Two perinatal outcomes, preterm birth and low birth weight were analyzed in this study and the definitions were given in the method part. We also use a flowchart to illustrate the study groups.

This was a retrospective case-control study of 135 singleton pregnant women with gestational hypertension or preeclampsia and their offspring who delivered in Renmin Hospital affiliated to Wuhan University from January 2015 to June 2017. All the information were collected from the electronic medical record system, such as age, gestational age, prenatal examination, neonatal information and neonatal complications, etc. Blood routine, hepatic and renal function, blood glucose, blood lipid, coagulation function and thyroid function were all completed by the laboratory department of the hospital. The primary outcome was the maternal and fetal complication, the second was the rate of thyroid dysfunction.

Inclusion criteria: 1. Maternal age between 20-40 years old; 2. No chronic diseases before pregnancy, such as chronic hypertension, cardiovascular and cerebrovascular diseases, autoimmune diseases (SLE etc.), thrombotic diseases, diabetes, thyroid endocrine diseases, hepatic and renal diseases, mental diseases, etc.; 3. The ultrasound confirmed that it was a single pregnancy; 4. Adequate iodine intake in daily diet; 5. Delivered in our hospital.
Exclusion criteria: 1. Pregnant women with history of thyroid related diseases before pregnancy and taking medicines for thyroid diseases; 2. Pregnant women with unhealthy diet habit; 3. Pregnant women who loss in follow-up; 4. Pregnant women without results of thyroid function test; 5. Pregnant women with diabetes or gestational diabetes or some other endocrine diseases.

Definitions

Women without pre-existing hypertension were classified as having pregnant induced hypertension (PIH) if they had a systolic blood pressure ≥140 mm Hg and/ or diastolic blood pressure ≥90 mm Hg on at least two occasions first occurring after 20 gestational weeks.

Preeclampsia was defined as gestational hypertension in combination with one or more of the following new-onset conditions: proteinuria (urinary protein dip sticks ≥1+ or ≥300 mg/24-hour); other maternal organ dysfunction, including renal insufficiency, liver involvement, neurological complications, and hematological complications; and uteroplacental dysfunction.

Preterm birth: Babies born before 37 gestational week.

Low birth weight: The birth weight is less than 2500g.

According to the guidelines for the management of thyroid disorders during pregnancy and postpartum issued by the American thyroid association in 2017, the definitions of thyroid diseases are as follows:

Clinical hypothyroidism: a. serum thyrotropic hormone (TSH) >4 mIU/L, and serum free thyroxine (FT4) < lower limit of normal reference b. serum TSH >10 mIU/L, with or without FT4 reduction.

Subclinical hypothyroidism: serum TSH >4 mIU/L but no more than 10 mIU/L, serum FT4 is within the reference range.

Hypothyroxinemia: serum FT4 < lower limit of normal reference value, and TSH is within the range of gestation-specific thyroid function reference value.

Gestational thyrotoxicosis: when TSH is less than 0.1 mIU/L, FT4 > gestational specific value reference upper limit.

Hashimoto thyroiditis: serum TPOAb ≥ 40 mIU/L.
Serum TSH, FT4, FT3 and TPOAb levels were measured using electrochemi-luminescence immunoassay (Cobas Elesys 601, Roche Diagnostics). The reference ranges of FT4 in our hospital is 0.89-1.8 ng/dL; the reference ranges of free triiodothyronine (FT3) in our hospital is 2.3-4.2 pg/mL.

Associations of thyroid dysfunction and preeclampsia with neonatal outcomes were assessed by logistic regression, unadjusted first, and then adjusted for age, gestational history, menstrual cycle, family history, history of gestational hypertension.

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?

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

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

* It is suggested to compare the outcomes of the groups in a separate table.

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

* 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.

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

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

* 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. In the revised manuscript, we have now given the full name of every abbreviation when it first appeared, reedited those confused sentences and added maternal outcomes in the result part. We also added all P values and specified all the values in the table 1 and 2. Associations of thyroid dysfunction and preeclampsia with neonatal outcomes were assessed by logistic regression, unadjusted first, and then adjusted for age, gestational history, menstrual cycle, family history, history of gestational hypertension.

Of the 135 participants, 30 were PIH, 20 were MPE, 85 were SPE. There were totally 7 cases of fetal growth restriction (FGR), 3 cases of placental abruption and 2 cases of pleural effusion in these participants. All 7 cases of FGR, 2 cases of pleural effusion and 2 cases of placental abruption occurred in patients with severe preeclampsia. Only one case of placental abruption was found in patients with mild preeclampsia. Table 1 presents the clinical, biochemical markers and the incidences of adverse neonatal outcomes among PIH, MPE and SPE. There were one abortion, two induced labor and two fetal death reported in SPE group. The gestational week and neonatal birth weight were significantly lower and the preterm birth rate was significantly higher in SPE when compared with other two groups (P<0.001). SPE group had significantly higher rate of thyroid dysfunction than MPE (P=0.01). Brain natriuretic peptide (BNP) was significantly higher in SPE group than in PIH group (P=0.002).

Table 2 shows the clinical, biochemical markers and the incidences of adverse neonatal outcomes among PIH, EPE and LPE. There were 57 EPE and 48 LPE. One abortion and two induced labor reported in EPE group. EPE and LPE both had one fetal death. There were 4 cases of FGR, 2 cases of placenta abruption and 2 cases of pleural effusion in patients with early onset preeclampsia. 3 cases of FGR and one case of placenta abruption occurred in patients with late onset preeclampsia. BNP was significantly higher in EPE group and LPE group than in PIH group (P=0.010, P=0.005). The gestational week and neonatal birth weight were significantly lower and the preterm birth rate was significantly higher in EPE when compared with other two groups (P<0.001). EPE group had the highest rate of thyroid dysfunction (71.9%).

The incidence of preterm birth and low birth weight was significantly higher in the participants with thyroid dysfunction than those without (49.3% vs. 25%, P=0.008; 45.1% vs. 27.1%, P=0.047). In the study population, preterm birth rate was positively associated with the 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), and negatively associated with the onset time of preeclampsia (OR=0.31, 95%CI [0.099, 0.110], P<0.001). The rate of low birth weight was positively associated with the 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), and negatively associated with the onset time of preeclampsia (OR=0.097, 95%CI [0.033, 0.282], P<0.001). Results of logistic regression analysis for thyroid dysfunction and fetal outcomes were in Table 3.
Response to comment #5

Discussion

* The first paragraph of the discussion section is not clear and needs to be edited.

* Please present some underlying pathophysiology associated with findings.

* 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?

* What are the strengths of the study?

* What further studies are recommended in this area?

We appreciate the comment from the reviewer. In the revised manuscript, we have now reedited the first paragraph of the discussion section and added the underlying pathophysiology associated with findings. We also analyzed other relevant researches in the discussion part and gave some expectations for further studies.

From the results, we found that patients with severe preeclampsia, early onset preeclampsia or thyroid dysfunction had more incidence of adverse maternal and fetal outcomes. The more severity the gestational hypertension disease was, the higher incidence the preterm birth, thyroid dysfunction and low neonatal birth weight. The earlier the preeclampsia occurred, the higher incidence the preterm birth, thyroid dysfunction and low neonatal birth weight. Our data show that the incidences 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 incidences 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.

Preeclampsia is one of the major causes of maternal and perinatal death. To better manage this disease, we need to improve our knowledge to better identify patients with preeclampsia at increased risk for adverse outcomes. In this study, most maternal adverse outcomes happened in patients with SPE or EPE. We found that BNP was significantly higher in these two groups which was in accordance with the symptoms. However, we did not find any difference among these groups in blood lipids.
Hypothyroidism has been shown to have various vascular effects, including endothelial cell dysfunction which is also a pathophysiological basis of gestational hypertension. A study included 16364 singleton births hypothyroid mothers in Finland found that maternal hypothyroidism was associated with 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 when maternal serum TSH > 10 mIU/L, the incidence of stillbirth was significantly increased. A study included 25756 women conducted by Casey et al. found that pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption (relative risk 3.0, 95% CI[1.1– 8.2]). Preterm birth was almost 2-fold higher in women with subclinical hypothyroidism (relative risk, 1.8, 95% CI[1.1–2.9]). Another study found that the incidence of premature birth, low birth weight and neonatal asphyxia in pregnant women with hyperthyroidism was significantly higher than that in normal pregnant women. However, 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. The incidence of hyperthyroidism is rare in this population. It might be due to the small sample size of the study and the different races of the participants.

Many studies focused only on the first trimester, and did not include all preeclampsia types. The present study investigated thyroid hormones of gestational hypertension women in the second half trimester and compared various types of preeclampsia according to the severity and the gestational age. Our results were also supported by other studies in the second half trimester. A study included 6031 mothers showed that if the thyroid hormones became normal after treating the women developing hypothyroidism in the first trimester, there is no significant differences in the risk of developing preeclampsia from the normal pregnant women. But 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. However, IMH identified in the second trimester was associated with increased risk of adverse pregnancy outcome. 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’s more, 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. Correspondingly, the rate of neonatal intensive care unit will be decreased and the burden of the family and society will reduce. Thus it might be helpful to test thyroid hormones in women with preeclampsia in all three stage and give treatment as early as possible to avoid adverse pregnant outcomes.
This is only a start. A lot of questions are still worth discussing, such as “Does thyroid dysfunction in the first half trimester or in the second trimester have a greater effect on maternal and fetal pregnancy outcomes?” “Whether the treatment needed for those with FT3 and FT4 both under the lower limit but normal TSH to prevent adverse neonatal outcomes?”, etc.

Responses to Reviewer #2

Response to comment #1

Patient flow is not clear: did the authors include consecutive patients. If not, how where they selected/excluded?

We thank the reviewer for the comment. In the revised manuscript, we have added the inclusion criteria and the exclusion criteria.

Inclusion criteria: 1. Maternal age between 20-40 years old; 2. No chronic diseases before pregnancy, such as chronic hypertension, cardiovascular and cerebrovascular diseases, autoimmune diseases (SLE etc.), thrombotic diseases, diabetes, thyroid endocrine diseases, hepatic and renal diseases, mental diseases, etc.; 3. The ultrasound confirmed that it was a single pregnancy; 4. Adequate iodine intake in daily diet; 5. Delivered in our hospital.

Exclusion criteria: 1. Pregnant women with history of thyroid related diseases before pregnancy and taking medicines for thyroid diseases; 2. Pregnant women with unhealthy diet habit; 3. Pregnant women who loss in follow-up; 4. Pregnant women without results of thyroid function test; 5. Pregnant women with diabetes or gestational diabetes or some other endocrine diseases.

Response to comment #2

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

We thank the reviewer for the comment. All the information were collected from the electronic medical record system during pregnancy. The thyroid function was 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).
Response to comment #3

Only data on TSH, FT3 and FT4 are provided. How did the authors diagnose specific conditions (e.g. Hashimoto's)? Where other lab tests performed? In all women. What are the reference values for TSH, FT3 and FT4 in the local population? Did the authors consider having a matched control group of uncomplicated pregnancies?

We thank the reviewer for the comment. Blood routine, hepatic and renal function, blood glucose, blood lipid, coagulation function and thyroid function were all completed by the laboratory department of the hospital. According to the guidelines for the management of thyroid disorders during pregnancy and postpartum issued by the American thyroid association in 2017, the definitions of thyroid diseases are as follows: Clinical hypothyroidism: a. serum thyrotropic hormone (TSH) > 4 mIU/L, and serum free thyroxine (FT4) < lower limit of normal reference b. serum TSH > 10 mIU/L, with or without FT4 reduction. Subclinical hypothyroidism: serum TSH > 4 mIU/L but no more than 10 mIU/L, serum FT4 is within the reference range. Hypothyroxinemia: serum FT4 < the lower limit of normal reference value, and TSH is within the range of gestation-specific thyroid function reference value. Gestational thyrotoxicosis: when TSH is less than 0.1 mIU/L, FT4 > gestational specific value reference upper limit. Hashimoto thyroiditis: serum TPOAb ≥ 40 mIU/L. The reference ranges of FT4 in our hospital is 0.89-1.8 ng/dL; the reference ranges of free triiodothyronine (FT3) in our hospital is 2.3-4.2 pg/mL. Because most of the uncomplicated pregnant women did not regularly perform the thyroid function test in the late trimester, so we did not include this control group.

Response to comment #4

Multiple comparisons are performed: did the authors using Bonferroni correction or similar?

We thank the reviewer for the comment. We have used adjusted P value for multiple comparisons in chi-square test and Kruskal Wallis Test.

Response to comment #5

What is the dependent variable for the logistic regression analysis shown in Table 3? Preterm birth, low birth weight or both? A logistic regression analysis with 7 independent variables would require some 70 pregnancies with the adverse outcome to predicted to be reliable.

We thank the reviewer for the comment. The dependent variable for the logistic regression analysis were preterm birth and low birth weight, unadjusted first, and then adjusted for age, gestational history, menstrual cycle, family history, history of gestational hypertension.
Response to comment #6

The conclusion that "monitoring thyroid hormones in women with preeclampsia might give us a clue to give treatment as early as possible to avoid adverse neonatal outcomes" is not substantiated by study findings.

We thank the reviewer’s comment. We have reedited the conclusion. SPE and EPE had more incidence of preterm birth and lower neonatal birth weight than MPE and LPE. Patients with thyroid dysfunction are more prone to preterm birth. Therefore, monitoring thyroid hormones in women with preeclampsia might help us to predict adverse neonatal outcomes.