

Association between thyroid hormone parameters during early pregnancy and gestational hypertension: a prospective cohort study

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Abstract

Objective: Thyroid dysfunction may play a role in the development of gestational hypertension. However, this relationship remains unclear. This study was performed to evaluate the association between thyroid hormone parameters during early pregnancy and gestational hypertension.

Methods: Women with singleton pregnancies were recruited into this prospective cohort study at 9 to 13 gestational weeks, and their serum thyroid-stimulating hormone, free thyroxine, and free triiodothyronine concentrations were measured using electrochemiluminescence immunoassays. In total, 1226 participants were included in the final analysis.

Results: Of the 1226 participants, 81 subsequently developed gestational hypertension (overall incidence of 6.6%). Compared with women with euthyroidism, both pregnant women with hypothyroidism and those with subclinical hypothyroidism had an increased risk of gestational hypertension (adjusted odds ratio [OR], 3.61; 95% confidence interval [CI], 1.52–8.57 and OR, 2.24; 95% CI, 1.06–4.72, respectively). When the thyroid-stimulating hormone and free thyroxine concentrations were analyzed by quintiles, the women in the highest thyroid-stimulating hormone quintile had a higher risk of gestational hypertension (adjusted OR, 4.22; 95% CI, 1.78–9.05) than the women in the middle quintile.

Conclusion: Our results suggest that hypothyroidism, subclinical hypothyroidism, and a high thyroid-stimulating hormone concentration during early pregnancy are risk factors for gestational hypertension.

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Keywords

Thyroid function, hypothyroidism, subclinical hypothyroidism, gestational hypertension, pregnancy, thyroid-stimulating hormone

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Introduction

Maternal thyroid hormones play a critical role in maintaining systemic homeostasis and have been shown to be associated with many health-related effects in mothers and their children.¹ Several studies have shown that thyroid dysfunction is associated with hypertensive disorders during pregnancy.²⁻⁴ Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension (GH), preeclampsia, and eclampsia, with an estimated prevalence of 4% to 11% among pregnant women in China.^{5,6} GH is a major cause of maternal and infant morbidity and mortality. Some observational studies have shown that mothers with hypothyroidism have an increased risk of GH.⁷ However, other studies have shown less conclusive associations between milder forms of maternal thyroid dysfunction and GH.⁸ Most of these studies were conducted among Western populations and had a limited sample size. Furthermore, numerous studies on this topic have also been published in the last decade. Since 2016, the two-child policy was fully implemented in China, and pregnancy at advanced maternal age has become more common. This has caused new challenges in pregnancy management and treatment of pregnancy complications.⁹ The incidence of GH is significantly higher than that prior to implementation of the two-child policy, and this trend may be related to increased maternal age.¹⁰ International scientific society guidelines also consider a maternal age of >30

years to be a risk factor for hypothyroidism in pregnancy, and screening for thyroid function is recommended.^{11,12} However, few studies have focused on the relationship between maternal thyroid function and GH. In this epidemiological study, we estimated the associations between thyroid function during early pregnancy and GH.

Material and methods

Ethics statement

The protocol and design of this prospective cohort study were approved by the hospital ethics and scientific committees of the Jiangxi Maternal and Child Health Hospital, Nanchang, China. All participants provided written informed consent.

Study design and participants

From May 2015 to September 2017, participants were recruited at their prenatal visit at Jiangxi Maternal and Child Health Hospital. The inclusion criteria were a hospital visit at the 9th to 13th weeks of gestation, singleton pregnancy, and planning to give birth in the study hospital. Pregnant women with chronic hypertension, a history of thyroid disease, and no thyroid measurements were excluded. Data on individual participants were collected using questionnaires during the 9th to 13th weeks of gestation. The pre-pregnancy weight and height were self-reported. In total, 1226 pregnant women were included in the final analysis.

Thyroid hormone measurements

Blood samples were collected at the outpatient clinic during the 9th to 13th weeks of gestation. Thyroid-related parameters, including the concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine, were measured using electrochemiluminescence immunoassays according to the manufacturer's protocols. The reference ranges for TSH and FT4 were calculated according to the 2.5th to 97.5th percentiles. Clinical thyroid dysfunction was defined as follows: hyperthyroidism (TSH of <0.3 mIU/mL and FT4 of >14.4 pmol/L), subclinical hyperthyroidism (TSH of <0.3 mIU/mL and normal FT4), hypothyroidism (TSH of >3 mIU/mL and FT4 of <7.9 pmol/L), and subclinical hypothyroidism (TSH of >3.0 mIU/mL and normal FT4).

Maternal GH

The diagnoses of GH and preeclampsia were obtained from the electronic medical records linked to the participant inpatient and outpatient records. GH and preeclampsia were clinically diagnosed according to the American College of Obstetricians and Gynecologists guidelines of 2013.¹³ Briefly, GH was defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg before 20 weeks of gestation with normal blood pressure. The outcome of GH was reconfirmed before delivery; that is, the diagnosis was not based only on a single outpatient visit or single blood pressure measurement. Preeclampsia was diagnosed using the above-mentioned criteria plus the presence of proteinuria (urine protein level of ≥ 0.3 g/24 hours). In the present study, data on GH and preeclampsia were analyzed together.

Statistical analysis

Normally distributed variables are expressed as mean \pm standard deviation and were compared using Student's t-test. The chi-square test or Fisher's exact test was used to compare proportions between the two groups. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of thyroid dysfunction with GH and the associations of TSH and FT4 quintiles with GH were estimated using logistic regression models adjusted for maternal age, education, parity, current delivery mode, pre-pregnancy body mass index, gestational weight gain, and newborn sex. All reported p-values were two-sided, and p-values of <0.05 were considered statistically significant. The statistical analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Of 1226 pregnant women, 81 (6.6%) developed GH. The characteristics of the pregnant women with and without GH are shown in Table 1. Compared with women without GH, women with GH were more likely to have advanced maternal age and higher pre-pregnancy body mass index. There were no significant differences in maternal education, delivery modes, or newborn sex between the two groups.

Compared with women with euthyroidism, the logistic regression analysis showed that both pregnant women with hypothyroidism and those with subclinical hypothyroidism had a higher risk of GH (adjusted OR, 3.61; 95% CI, 1.52–8.57 and adjusted OR, 2.24; 95% CI, 1.06–4.72, respectively). No associations were found between hyperthyroidism or subclinical hyperthyroidism and GH (Table 2). Further analysis of the risk of GH according to quintiles of the TSH level is presented in Table 3.

Table 1. Characteristics of pregnant women with and without GH (n = 1226).

Characteristics	Women without GH (n = 1145)	Women with GH (n = 81)	P value
Maternal age at birth, years	28.8 ± 4.7	30.1 ± 5.1	0.016
Education			
High school or less	165 (14.4)	19 (23.5)	0.088
College	444 (38.8)	28 (34.6)	
Undergraduate or above	536 (46.8)	34 (42.0)	
Gestational age at delivery, weeks	38.2 ± 2.1	35.6 ± 3.4	<0.001
Parity			
0	686 (59.9)	39 (48.1)	0.037
≥1	459 (40.1)	42 (51.9)	
Pre-pregnancy BMI, kg/m ²			
<18.5	237 (20.7)	13 (16.0)	0.021
18.5–25.0	783 (68.4)	51 (63.0)	
>25.0	125 (10.9)	17 (21.0)	
Gestational weight gain, kg	13.1 ± 4.7	12.9 ± 4.6	0.934
Delivery modes			
Vaginal delivery	946 (82.6)	60 (74.1)	0.053
Cesarean delivery	199 (17.4)	21 (25.9)	
Newborn sex			
Male	687 (60.0)	47 (58.0)	0.726
Female	458 (40.0)	34 (42.0)	
TSH, mIU/mL	1.12 ± 0.85	1.56 ± 1.33	0.014
FT4, pmol/L	15.20 ± 2.11	16.93 ± 3.08	0.705
FT3, pmol/L	6.94 ± 1.05	7.21 ± 2.14	0.355
Thyroid dysfunction			
Hypothyroidism	29 (2.5)	7 (8.6)	0.002
Subclinical hypothyroidism	62 (5.4)	9 (11.1)	0.061
Hyperthyroidism	18 (1.6)	3 (3.7)	0.153
Subclinical hyperthyroidism	27 (2.4)	4 (4.9)	0.201

Data are presented as n (%) for categorical variables and mean ± standard deviation for continuous variables.

BMI, body mass index; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; GH, gestational hypertension.

Women in the fifth quintile of TSH had a higher risk of GH (adjusted OR, 4.22; 95% CI, 1.78–9.05) than those in the third quintile. No significant associations between GH and FT4 were observed by analyzing FT4 defined by quintiles (Table 4).

Discussion

In this prospective cohort study, we evaluated the associations of maternal thyroid hormone parameters during early pregnancy

with GH. We found that hypothyroidism, subclinical hypothyroidism, and high TSH levels were associated with an increased risk of GH, findings that agree with those of previous studies.¹⁴ At present, universal thyroid screening during pregnancy remains controversial.¹⁵ Our study adds an important piece of evidence showing that early diagnosis and treatment may result in improved pregnancy outcomes.

In this population-based study, our results strengthen the notion of the

Table 2. Thyroid dysfunction and risk of gestational hypertension.

Thyroid dysfunction	n	n (%) with GH	OR (95% CI)	P value
Hypothyroidism	36	7 (19.4)	3.61 (1.52–8.57)	0.004
Subclinical hypothyroidism	71	9 (12.6)	2.24 (1.06–4.72)	0.033
Hyperthyroidism	21	3 (14.2)	2.26 (0.76–8.63)	0.161
Subclinical hyperthyroidism	31	4 (12.9)	1.87 (0.63–5.58)	0.258
Euthyroidism (reference)	1067	58 (5.4)	Reference	

ORs were adjusted for maternal age, education, parity, delivery mode, pre-pregnancy body mass index, gestational weight gain, and newborn sex.

GH, gestational hypertension; OR, odds ratio; CI, confidence interval.

Table 3. Risk of gestational hypertension by quintile categories of TSH.

TSH by quintile	n	n (%) with GH	OR (95% CI)	P value
Q1	242	11 (4.5)	1.26 (0.65–2.47)	0.574
Q2	247	16 (6.4)	2.23 (0.87–4.68)	0.104
Q3 (reference)	241	10 (4.1)	Reference	
Q4	247	18 (7.3)	2.72 (0.91–5.74)	0.092
Q5	249	26 (10.4)	4.22 (1.78–9.05)	0.001

ORs were adjusted for maternal age, education, parity, delivery mode, pre-pregnancy body mass index, gestational weight gain, and newborn sex.

TSH, thyroid-stimulating hormone; GH, gestational hypertension; OR, odds ratio; CI, confidence interval.

Table 4. Risk of gestational hypertension by quintile categories of FT4.

FT4 by quintile	n	n (%) with GH	OR (95% CI)	P value
Q1	244	21 (8.6)	1.37 (0.61–2.62)	0.404
Q2	246	18 (7.3)	1.26 (0.58–2.91)	0.551
Q3 (reference)	246	14 (5.6)	Reference	
Q4	244	15 (6.1)	1.18 (0.57–2.49)	0.652
Q5	246	13 (5.3)	1.11 (0.52–2.33)	0.791

ORs were adjusted for maternal age, education, parity, delivery mode, pre-pregnancy body mass index, gestational weight gain, and newborn sex.

GH, gestational hypertension; OR, odds ratio; CI, confidence interval; FT4, free thyroxine.

association between hypothyroidism and GH.¹⁶ Thyroid hormones are essential for maintaining homeostasis as evidenced by the myriad effects of thyroid hormone deficiency. Hypothyroidism significantly interferes with the cardiovascular system, leading to changes in left ventricular function, decreased cardiac output, and

increased systemic vascular resistance.¹⁷ Although some observational studies have demonstrated associations between subclinical hypothyroidism and hypertensive disorders during pregnancy, limited sample sizes and conflicting results have been reported.^{18,19} Wilson et al.²⁰ found that subclinical hypothyroidism was associated with

an increased risk of GH. A meta-analysis showed that subclinical hypothyroidism was associated with several adverse pregnancy outcomes, including placental abruption, premature rupture of membranes, and neonatal death; however, it did not show an increased risk of GH.²¹ Our study showed that various types of thyroid dysfunction have various effects on GH in pregnancy. Several studies have revealed that hyperthyroidism and high FT4 levels are risk factors for hypertensive disorders during pregnancy.^{7,22} While our study included a relatively large sample size, few patients had hyperthyroidism, attributable to the lack of statistical power to produce this finding.

When the TSH and FT4 levels were analyzed using the entire range, we found a significant positive association between the highest TSH quintile (but not the highest FT4 quintile) and the risk of GH. Thyroid hormones act directly to increase peripheral resistance and endothelial dysfunction, causing GH.^{23–25} Our study does not agree with the findings of the Generation R Study, a prospective cohort study showing that high FT4 but not TSH levels during early pregnancy were associated with a significantly increased risk of hypertensive disorders.²² These differing results might be partially attributable to the study population consisting of pregnant women. In the Generation R Study, the incidence of overt hyperthyroidism was relatively high, while hypothyroidism was rare; this is in contrast to the results of our study. The lack of significant findings may also be due to the small sample size. A major limitation of our study is that the TSH and FT4 levels were only tested in early pregnancy. The current study was conducted in one specific region of China; therefore, generalizability to the entire population is limited. Only the diagnosis of GH was obtained from the electronic medical records; the systolic blood pressure and diastolic blood pressure were not extracted.

We were unable to examine the associations of thyroid hormone parameters and the continuous variable of blood pressure.

Conclusions

Our results support those of previous studies showing that hypothyroidism, subclinical hypothyroidism, and a high TSH level during early pregnancy are risk factors for GH. Future research will clarify whether women at risk of GH benefit from thyroid medication during early pregnancy.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Saki F, Dabbaghmanesh MH, Ghaemi SZ, et al. Thyroid function in pregnancy and its influences on maternal and fetal outcomes. *Int J Endocrinol Metab* 2014; 12: e19378.
2. Ramtahal R and Dhanoo A. Subclinical hypothyroidism causing hypertension in pregnancy. *J Am Soc Hypertens* 2016; 10: 691–693.
3. Ashoor G, Maiz N, Rotas M, et al. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent development of preeclampsia. *Prenat Diagn* 2010; 30: 1032–1038.
4. Han Y, Mao LJ, Ge X, et al. Thyroid auto-antibodies in pregnancy are associated with hypertensive disorders of pregnancy: Ma'anshan Birth Cohort Study. *Clin Endocrinol (Oxf)* 2018; 88: 928–925.

5. Shen H, Liu X, Chen Y, et al. Associations of lipid levels during gestation with hypertensive disorders of pregnancy and gestational diabetes mellitus: a prospective longitudinal cohort study. *BMJ Open* 2016; 6: e013509.
6. Zhu YC, Yang HX, Wei YM, et al. Analysis of correlation factors and pregnancy outcomes of hypertensive disorders of pregnancy - a secondary analysis of a random sampling in Beijing, China. *J Matern Fetal Neonatal Med* 2017; 30: 751–754.
7. Mannisto T, Mendola P, Grewal J, et al. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. *J Clin Endocrinol Metab* 2013; 98: 2725–2733.
8. Mannisto T, Vaarasmaki M, Pouta A, et al. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. *J Clin Endocrinol Metab* 2010; 95: 1084–1094.
9. Cheng PJ and Duan T. China's new two-child policy: maternity care in the new multiparous era. *BJOG* 2016; 123: 7–9.
10. Zhang HX, Zhao YY and Wang YQ. Analysis of the characteristics of pregnancy and delivery before and after implementation of the two-child policy. *Chin Med J (Engl)* 2018; 131: 37–42.
11. Dieguez M, Herrero A, Avello N, et al. Prevalence of thyroid dysfunction in women in early pregnancy: does it increase with maternal age? *Clin Endocrinol* 2016; 84: 121–126.
12. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; 97: 2543–2565.
13. Roberts JM, August PA, Bakris G, et al. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; 122: 1122–1131.
14. Akram FH, Johansson B, Mollerstrom G, et al. Incidence of subclinical hypothyroidism and hypothyroidism in early pregnancy. *J Womens Health* 2017; 26: 1231–1235.
15. Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017; 27: 315–389.
16. Shinohara DR, Santos TDS, de Carvalho HC, et al. Pregnancy complications associated with maternal hypothyroidism: a systematic review. *Obstet Gynecol Surv* 2018; 73: 219–230.
17. Kattah A and Garovic VD. Subclinical hypothyroidism and gestational hypertension: causal or coincidence? *J Am Soc Hypertens* 2016; 10: 688–690.
18. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005; 105: 239–245.
19. Sahu MT, Das V, Mittal S, et al. Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. *Arch Gynecol Obstet* 2010; 281: 215–220.
20. Wilson KL, Casey BM, McIntire DD, et al. Subclinical thyroid disease and the incidence of hypertension in pregnancy. *Obstet Gynecol* 2012; 119: 315–320.
21. Maraka S, Ospina NM, O'Keefe DT, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. *Thyroid* 2016; 26: 580–590.
22. Medici M, Korevaar TI, Schalekamp-Timmermans S, et al. Maternal early-pregnancy thyroid function is associated with subsequent hypertensive disorders of pregnancy: the generation R study. *J Clin Endocrinol Metab* 2014; 99: E2591–E2598.
23. Virdis A, Colucci R, Fornai M, et al. Inducible nitric oxide synthase is involved in endothelial dysfunction of mesenteric small arteries from hypothyroid rats. *Endocrinology* 2009; 150: 1033–1042.
24. Dernellis J and Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. *Am Heart J* 2002; 143: 718–724.
25. Zaveljcina J, Legan M and Gaberscek S. Newly diagnosed hyperthyroidism in the 25th gestational week of pregnancy presenting with systolic arterial hypertension only. *J Obstet Gynaecol* 2016; 36: 529–530.