Subclinical hypothyroidism during pregnancy and the impact of LT4 therapy on pregnancy outcomes in women (#108727)

First submission

Guidance from your Editor

Please submit by **2 Feb 2025** for the benefit of the authors (and your token reward) .

Structure and Criteria
Please read the 'Structure and Criteria' page for guidance.

Custom checks
Make sure you include the custom checks shown below, in your review.

Raw data check
Review the raw data.

Image check
Check that figures and images have not been inappropriately manipulated.

If this article is published your review will be made public. You can choose whether to sign your review. If uploading a PDF please remove any identifiable information (if you want to remain anonymous).

Files

Download and review all files from the materials page.

2 Figure file(s)
6 Table file(s)
1 Raw data file(s)

Custom checks

Human participant/human tissue checks

- Have you checked the authors ethical approval statement?
- Does the study meet our article requirements?
- Has identifiable info been removed from all files?
- Were the experiments necessary and ethical?

Clinical trial checks

- Have you checked the authors ethical approval statement?
- Does the study meet our article requirements?
- Is the statistical analysis correct, well powered etc?

Structure and Criteria

Structure your review

The review form is divided into 5 sections. Please consider these when composing your review:

1. **BASIC REPORTING**
2. **EXPERIMENTAL DESIGN**
3. **VALIDITY OF THE FINDINGS**
4. General comments
5. Confidential notes to the editor

You can also annotate this PDF and upload it as part of your review

When ready submit online.

Editorial Criteria

Use these criteria points to structure your review. The full detailed editorial criteria is on your guidance page.

BASIC REPORTING

- Clear, unambiguous, professional English language used throughout.
- Intro & background to show context. Literature well referenced & relevant.
- Structure conforms to PeerJ standards, discipline norm, or improved for clarity.
- Figures are relevant, high quality, well labelled & described.
- Raw data supplied (see PeerJ policy).

EXPERIMENTAL DESIGN

- Original primary research within Scope of the journal.
- Research question well defined, relevant & meaningful. It is stated how the research fills an identified knowledge gap.
- Rigorous investigation performed to a high technical & ethical standard.
- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- **Impact and novelty is not assessed.** Meaningful replication encouraged where rationale & benefit to literature is clearly stated.
- All underlying data have been provided; they are robust, statistically sound, & controlled.
- Conclusions are well stated, linked to original research question & limited to supporting results.

Standout reviewing tips

The best reviewers use these techniques

Tip	*Example*
Support criticisms with evidence from the text or from other sources	*Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.*
Give specific suggestions on how to improve the manuscript	*Your introduction needs more detail. I suggest that you improve the description at lines 57- 86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).*
Comment on language and grammar issues	*The English language should be improved to ensure that an international audience can clearly understand your text. Some examples where the language could be improved include lines 23, 77, 121, 128 – the current phrasing makes comprehension difficult. I suggest you have a colleague who is proficient in English and familiar with the subject matter review your manuscript, or contact a professional editing service.*
Organize by importance of the issues, and number your points	*1. Your most important issue* *2. The next most important item* *3. …* *4. The least important points*
Please provide constructive criticism, and avoid personal opinions	*I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC*
Comment on strengths (as well as weaknesses) of the manuscript	*I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.*

Subclinical hypothyroidism during pregnancy and the impact of LT4 therapy on pregnancy outcomes in women

Yutian Zhou [Equal first author, 1, 2], **Yi Wang** [Equal first author, 3], **Tianxiao Yu** [1], **Yuan Li** [4], **Meiyan Mi** [5], **Jianqiang Su** [4], **Jun Ge** [Corresp. 1, 2]

[1] Research Center for Clinical Medical Sciences, The Fourth Hospital of Shijiazhuang, Shijiazhuang, China

[2] School of Public Health, Hebei Medical University, Shijiazhuang, Select..., China

[3] Department of Clinical Laboratory, The Fourth Hospital of Shijiazhuang, Shijiazhuang, China

[4] Department of Medicine, The Fourth Hospital of Shijiazhuang, Shijiazhuang, China

[5] Department of Gynecology, The Fourth Hospital of Shijiazhuang, Shijiazhuang, China

Corresponding Author: Jun Ge
Email address: GJ8005AA@163.com

Aims: The purpose of this study is to investigate the impact of subclinical hypothyroidism (SCH) during pregnancy and levothyroxine (LT4) therapy on pregnancy outcomes.**Methods:** Among 6510 pregnant women who came to The Fourth Hospital of Shijiazhuang for pregnancy examination and delivery, 266 pregnant women with SCH and treated with LT4 were selected as the observation group and 672 pregnant women without SCH were selected as the control group, and the incidence rates of adverse pregnancy outcomes in pregnant women and newborns of the two groups were compared using Chi-square test and logistic regression. Pregnant women treated with LT4 were categorized into SCH cured and not cured groups and compared with the control group using chi-square test. The correlation of TSH levels at different stages of pregnancy was explored using Spearman's rank test.**Results:** The incidence of hypertensive disorders of pregnancy (HDP), premature rupture of membranes (PROM), neonatal Ventricular or Atrial septal defect (V/ASD), hyperbilirubinemia, and pneumonia was higher in the observation group (SCH pregnant women) than in the control group (non-SCH pregnant women) ($p<0.05$). The incidence of multiple pregnancy complications was higher in the SCH non-cured group (SCH in two or three gestational stages) compared to the observation group. with a tendency for TSH levels to increase as the pregnancy progressed.**Conclusion:** SCH during pregnancy is associated with a high incidence of various pregnancy complications, and standardized LT4 therapy that controls serum TSH levels at normal levels throughout pregnancy can reduce these risks.

Subclinical hypothyroidism during pregnancy and the impact of LT4 therapy on pregnancy outcomes in women

Yutian Zhou[1, 2, †], Yi Wang[3 †], Tianxiao Yu[1], Yuan Li[4], Meiyan Mi[5], Jianqiang Su[4], Jun Ge[1, 2,*]

[1] Research Center for Clinical Medical Sciences, The Fourth Hospital of Shijiazhuang, Shijiazhuang, 050000, China.

[2] School of Public Health, Hebei Medical University, Shijiazhuang, 050000, China

[3] Department of Clinical Laboratory, The Fourth Hospital of Shijiazhuang, Shijiazhuang, 050000, China.

[4] Department of Medicine, The Fourth Hospital of Shijiazhuang, Shijiazhuang, 050000, China.

[5] Department of Gynecology, The Fourth Hospital of Shijiazhuang, Shijiazhuang, 050000, China.

.

[†] Contributed equally

[*] Corresponding author, Jun Ge, The Fourth Hospital of Shijiazhuang, No.16 Tangu North Street, Chang'an District, Shijiazhuang, Hebei, China.

Phone Number: 0311-89927360. E-mail: GJ8005AA@163.com

Abstract

Aims: The purpose of this study is to investigate the impact of subclinical hypothyroidism (SCH) during pregnancy and levothyroxine (LT4) therapy on pregnancy outcomes.

Methods: Among 6510 pregnant women who came to The Fourth Hospital of Shijiazhuang for pregnancy examination and delivery, 266 pregnant women with SCH and treated with LT4 were selected as the observation group and 672 pregnant women without SCH were selected as the control group, and the incidence rates of adverse pregnancy outcomes in pregnant women and newborns of the two groups were compared using Chi-square test and logistic regression. Pregnant women treated with LT4 were categorized into SCH cured and not cured groups and compared with the control group using chi-square test. The correlation of TSH levels at different stages of pregnancy was explored using Spearman's rank test.

Results: The incidence of hypertensive disorders of pregnancy (HDP), premature rupture of membranes (PROM), neonatal Ventricular or Atrial septal defect (V/ASD), hyperbilirubinemia, and pneumonia was higher in the observation group (SCH pregnant women) than in the control group (non-SCH pregnant women) ($p<0.05$). The incidence of multiple pregnancy complications was higher in the SCH non-cured group (SCH in two or three gestational stages) compared to the observation group. with a tendency for TSH levels to increase as the pregnancy progressed.

Conclusion: SCH during pregnancy is associated with a high incidence of various pregnancy complications, and standardized LT4 therapy that controls serum TSH levels at normal levels throughout pregnancy can reduce these risks.

Keywords: Pregnancy, Subclinical hypothyroidism, Levothyroxine therapy, Pregnancy outcome

Introduction

Thyroid disease is one of the most common endocrine disorders in clinical practice, with the highest prevalence in women, especially those of childbearing age [1]. SCH is a disorder characterised by high serum TSH levels and normal free thyroxine (FT4) levels, and is a common clinical condition during pregnancy. If left untreated, it may lead to further thyroid dysfunction, which can affect normal pregnancy and even endanger maternal and neonatal health

and safety [2]. Regarding the harms of SCH, numerous studies have shown that untreated patients with SCH have a higher risk of one or more adverse pregnancy outcomes (pregnancy loss, preterm birth (PTB), hypertension and low birth weight (LBW)) compared to pregnant women with normal thyroid function [3-7]. A retrospective cohort study of Chinese in 2019 showed that SCH during pregnancy increased the risk of hypertensive disorders of pregnancy (HDP), especially among women diagnosed with the disease in the first and second trimesters [8]. However, some other studies have not found any association between SCH and pregnancy complications [9-12].

Due to ethnic and regional differences, the American Thyroid Association (ATA) recommends that each regional units establish a specific reference range for serum TSH levels during pregnancy. If not, it is recommended that the upper limit of the reference value for serum TSH levels in the first trimester of pregnancy be established at 4.0 mIU/L [13]. LT4 therapy is currently commonly used to treat SCH during pregnancy. The aim is to keep serum TSH levels within the normal range[14,15]. Nevertheless, there is a lack of supporting evidence for the benefit of LT4 therapy in improving health status of pregnant women with SCH. A 2016 Meta-analysis on SCH in pregnancy showed that there was insufficient evidence to support that patients with SCH in pregnancy can benefit from LT4 therapy [16]. A study in 2022 showed that this benefit was influenced by the treatment time for pregnant women [17].

As of 2022, China has 19 free pre-conception and pregnancy examination, including thyroid function tests. Universal thyroid function screening during pregnancy remains controversial in other countries. Therefore, previous studies on the benefits of LT4 therapy on pregnancy outcomes in SCH patients during pregnancy favored starting LT4 therapy towards the end of the first trimester [18]. SCH status in pregnant women may not be detected in time, and the effect of LT4 therapy may be diminished. Furthermore, we found that previous studies have tended to focus on a short period after LT4 treatment and have not addressed the entire subsequent gestation period. The thyroid function status of pregnant women may have been incorrectly assessed.

The results of a 2018 survey showed a significant increase in the prevalence of SCH in china over the past decade or so, with a similar increase in the TPO-Ab-positive people [19]. The disease burden associated with subclinical hypothyroidism is increasing. In this context, a retrospective cohort study was conducted to investigate the impact of SCH in pregnancy on maternal and neonatal pregnancy outcomes and to explore the benefits of timely and standardised LT4 therapy for SCH on pregnancy outcomes. This study will provide a basis for the management of SCH in pregnancy.

Materials and Methods

Research object

From January 2019 to December 2020, a total of 938 pregnant women who underwent obstetric examinations and deliveries at the The Fourth Hospital of Shijiazhuang were invited to participate in this study. We applied the following inclusion criteria: (1) age 18–45; (2) no family history of psychiatric disorders; (3) Data of thyroid function test in three pregnancy stages. The exclusion criteria were as follows: (1) pre-pregnancy diabetes, hypertension; (2) abortion; (3) History of hyperthyroidism, hypothyroidism, thyroid surgery and LT4 treatment; (4)Twin or multiple, In Vitro Fertilization and Embryo Transfer(IVF-ET) Pregnancies; (5)Birth history of stillbirths and malformations. Subjects were treated with LT4 immediately if they were first diagnosed with SCH. Diagnostic criteria for SCH in pregnancy: serum TSH level >4.0 mIU/L, FT4 level : 12-22 pmol/L [20]. The serum test of thyroid function was performed by radioimmunotherapy in our laboratory. Ultimately, 672 women without SCH in pregnancy were included in the control group and 266 women with SCH in pregnancy were included in the observation group. 47 of the study subjects developed SCH in at least two stages of pregnancy and were included in the non-cured group: 12 pregnant women with SCH during the first and second trimesters, 11 pregnant women with SCH during the first and third trimesters, 16 pregnant women with SCH during the second and third trimesters, 8 pregnant women with SCH during all three stages of pregnancy. All the participants were informed about the study and a signed permission document was obtained in accordance with the Declaration of Helsinki. The

Ethics Committee of Shijiazhuang Obstetrics and Gynecology Hospital approved the study (NO.20230109). Figure 1 showed the details.

Data collection

The following questions were asked of the study participants through an electronic questionnaire. The questions included: maternal age, height, pre-pregnancy weight, education, parity, family income, family history of diabetes, smoking or exposure to secondhand smoke, alcohol consumption during pregnancy, folic acid, vitamin supple mentation and so on.

Adverse Pregnancy Outcome Collection: Pregnant women: gestational diabetes mellitus (GDM); HDP (including pre-eclampsia and eclampsia); premature rupture of membranes (PROM). Newborn: PTB; AWB (LBW and large babies); hyperbilirubinemia and other adverse neonatal events (RDS etc.). GDM is diagnosed based on the results of the 75 g OGTT at 24–28 weeks of gestation when the blood glucose met at least one of the following criteria: fasting plasma glucose (FPG) 5.1–6.9 mmol/L, 1 hr plasma glucose (PG1H) ⩾10 mmol/L, or 2 hr plasma glucose (PG2H) 8.5–11 mmol/L. PTB is defined as live births prior to completion of 37 weeks of gestation. AWB is defined as a newborn weighing more than 4000g or less than 2500g. The diagnostic criteria for other diseases are mainly based on the 2008 People's Health Press *Chinese Obstetrics and Gynaecology* [21].

Statistical analysis

SPSS 22.0 statistical software was used to analyse the data. For measured data, the mean ± standard deviation was used to describe the data, and the count data were described as the number of cases (%). The χ^2-test or Fisher's exact test were used to compare pregnancy outcomes between the different groups. The association between subclinical hypothyroidism in pregnancy and adverse pregnancy outcomes was further examined using a multifactorial logistic regression model, after adjusting for confounding factors such as age and pre-pregnancy BMI. Spearman correlation analysis was used to assess the relationship between TSH levels at different trimesters. All statistical tests were performed using a two-sided test, and p-Value <0.05

was considered statistically significant.

Results

Table 1 describes the baseline characteristics of the participants. There was no statistically significant difference in any of the characteristic indicators between the observation and control groups ($p > 0.05$).

Table 2 shows the occurrence of maternal and neonatal pregnancy outcomes in the observation and control groups. In terms of pregnant women, the observation group had a higher prevalence of HDP and PROM ($p<0.05$). In terms of newborns, the proportion of newborns with V/ASD, hyperbilirubinemia, and pneumonia was higher in the observation group ($p<0.05$). For other outcomes, no significant differences were found between the two groups.

Compared with non-SCH pregnant women in the same period, pregnant women with SCH in the first trimester had higher rates of GDM, HDP, neonatal pneumonia. Pregnant women with SCH in the second trimester had higher rates of HDP, PTB, AWB, hyperbilirubinemia and RDS. Pregnant women with SCH in the third trimester have higher rates of PTB. ($p< 0.05$). Table 3 showed the details.

Table 4 shows the results of a multifactorial logistic regression of SCH in pregnancy and five adverse pregnancy outcomes. The results of model 3, which adjusted for other factors such as age and BMI, showed that SCH in pregnancy was associated with a higher risk of hyperbilirubinemia and neonatal pneumonia.

Table 5 shows the comparison of pregnancy outcomes between the cured, the non-cured and control group of SCH during pregnancy. The attack rate of HDP, PROM, PTB, AWB, hyperbilirubinemia, V/ASD, and RDS was higher in the uncured group as compared to the control group, whereas there was no statistically significant difference between the cured group and the control group.

Table 6 shows the results of Spearman's rank correlation of TSH levels in different trimesters and in the entire population, TSH levels in the latter trimester were positively correlated with TSH levels in the previous trimester. In the control group, the population without

SCH, showed the same results. The highest correlation was found between TSH levels in the second and third trimester. Figure 2 shows the positive correlation of TSH levels between different trimesters in the control group (those without SCH).

Discussion

A single-center study was designed to evaluate the impact of SCH on pregnancy outcomes and the benefits of LT4 treatment for SCH on pregnancy outcomes. The study found that while all participants received LT4 treatment after diagnosis of SCH in pregnancy. However, there was an increased incidence of HDP, PROM, V/ASD and hyperbilirubinemia compared to normal pregnancies. The correlation between SCH diagnosed in different trimesters and pregnancy outcomes varied, and since GDM is diagnosed in the second trimester and hypertensive disorders of pregnancy also tend to occur in the second and third trimesters, the present study found that GDM was associated with SCH only in the first trimester. A Meta-analysis showed that SCH in pregnancy was associated with an increased risk of HDP regardless of the stage of pregnancy [22]. However, the present study found that the increased risk of HDP was only associated with SCH in the first and second trimesters of pregnancy, but not in the third trimester. This may be related to the subsequent treatment after the disease is detected.

Thyroid hormones have cardiovascular regulatory effects and chronic thyroid hormone disorders can lead to cardiovascular dysfunction [23-27]. A molecular study has also shown that patients with SCH have reduced nitric oxide secretion and impaired endothelium-associated vasodilatation [28], which leads to increased blood pressure. The impact of SCH in pregnancy on the newborn, a 2019 Meta-analysis on thyroid function in pregnancy and PTB showed that SCH was significantly associated with a higher risk of PTB [29]. In this study, we found that pregnant women with SCH had a higher incidence of PTB in both the second and third trimesters of pregnancy compared to non-SCH pregnant women. Preterm infants are often associated with a range of complications such as low birth weight and RDS.

In this study, 47 (5.01) pregnant women developed SCH in at least two trimesters. A comparison of the non-cured, cured and control groups showed that the non-cured group had a

higher risk of HDP, PROM, PTB, AWB, Hyperbilirubinemia, V/ASD and RDS than the control group. There was no statistical difference between the cured and control groups. This suggests that standardised LT4 therapy, which keeps maternal thyroid function at normal levels throughout the pregnancy cycle, is effective in reducing the risk of pregnancy-related adverse events. In compiling the data, we also found the phenomenon that LT4 therapy was highly effective, with normal thyroid function test data once or twice after dosing. However, after two to three months, SCH is prone to recurrence for the remainder of the current pregnancy, due to irregular medication or maternal discontinuation. This also reminds us that multiple thyroid function tests during pregnancy are necessary to detect abnormal thyroid function, to treat with LT4 in a timely manner, especially in pregnant women who already have abnormal thyroid function. The results of correlation of TSH levels at different stages of pregnancy showed a tendency to increase with increasing gestational weeks, and a recent retrospective study showed similar results[30]. Therefore, thyroid function monitoring during pregnancy and timely intervention is necessary to treat pregnant women whose TSH levels have exceeded or are close to the upper limit of the reference value.

In contrast to other studies, this study focused on the dynamics of thyroid function throughout pregnancy in the study population, particularly in the period after LT4 treatment was administered. LT4 treatment was able to correct the state of abnormal thyroid function, affirming the effectiveness of LT4 treatment for SCH. The results of the subgroup comparison, which varied according to the therapeutic control of SCH, showed that standardised and effective LT4 treatment, which resulted in SCH being cured and not recurring for the remainder of the current pregnancy, was beneficial for maternal and neonatal pregnancy outcomes. Of course, as a single-centre study involving only pregnant women who came to Shijiazhuang Obstetrics and Gynecology Hospital for examinations and deliveries, there may be subject to selection bias. Also, the sample size was small compared to other large cohort studies. Larger prospective studies are needed to validate our conclusions.

Conclusions

Therefore, necessary thyroid function screening and monitoring are recommended for women preparing for pregnancy and during pregnancy. For pregnant women who already have subclinical hypothyroidism, timely and standardised LT4 therapy will not only improve thyroid function, but also benefit both the mother and newborn in pregnancy.

Article information and declarations

Data Availability Statement

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

Ethics approval and consent to participate

The Ethics Committee of The Fourth Hospital of Shijiazhuang approved the study (No:20230109). All the participants were informed about the study and a signed permission document was obtained in accordance with the Declaration of Helsinki.

Contributions

Conception and design: Yutian Zhou and Yi Wang. Acquisition of data: All authors. Analysis and Interpretation of data: Yutian Zhou, Yi Wang and Tianxiao Yu. Drafting of the manuscript: Yutian Zhou. Critical revision of the manuscript for important intellectual content: Yi Wang and Tianxiao Yu. Statistical analysis: Yutian Zhou, Yi Wang and Tianxiao Yu. Obtaining funding: Jun Ge. Administrativetechnical or material support: Tianxiao Yu, Yuan Li, Meiyan Mi, Jianqiang Su and Jun Ge. Supervision: Jun Ge. Yutian Zhou and Yi Wang contributed equally to this work.

Funding

This work was funded by the Key Science and Technology Research Programme of the Hebei Provincial Health and Wellness Commission (No. 20191430).

Acknowledgments

We would thank patients and their family for this research understanding.

Conflflict of Interest

The authors declared that they have no conflflicts of interest.

References

[1] Wu Q, Rayman MP, Lv H, et al. (2015). Low Population Selenium Status Is Associated With Increased Prevalence of Thyroid Disease. The Journal of clinical endocrinology and metabolism, 100(11), 4037–4047. https://doi.org/10.1210/jc.2015-2222

[2]Hammond KR, Cataldo NA, Hubbard JA, et al. (2015). Gestational hypothyroidism: development of mild hypothyroidism in early pregnancy in previously euthyroid women. Fertility and sterility, 103(6), 1532–6.e1. https://doi.org/10.1016/j.fertnstert.2015.03.006

[3] Negro R, Schwartz A, Gismondi R, et al. (2010). Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. The Journal of clinical endocrinology and metabolism, 95(9), E44–E48. https://doi.org/10.1210/jc.2010-0340

[4] Casey BM, Dashe JS, Wells CE, et al. (2005). Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 105:239–245. https://doi.org/10.1097/01.AOG.0000152345.99421.22

[5] Wilson KL, Casey BM, McIntire DD, et al. (2012). Subclinical thyroid disease and the incidence of hypertension in pregnancy. Obstetrics and gynecology, 119(2 Pt 1), 315–320. https://doi.org/10.1097/AOG.0b013e318240de6a

[6] Schneuer FJ, Nassar N, Tasevski V, et al. (2012). Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes. The Journal of clinical endocrinology and metabolism, 97(9), 3115–3122. https://doi.org/10.1210/jc.2012-1193

[7] Chen LM, Du WJ, Dai J, Zhang Q, et al. (2014). Effects of subclinical hypothyroidism on maternal and perinatal outcomes during pregnancy: a single-center cohort study of a Chinese population. PloS one, 9(10), e109364. https://doi.org/10.1371/journal.pone.0109364

[8] Wu MQ, Liu J, Wang YQ, et al. (2019). The Impact of Subclinical Hypothyroidism on Adverse Perinatal Outcomes and the Role of Thyroid Screening in Pregnancy. Frontiers in endocrinology, 10, 522. https://doi.org/10.3389/fendo.2019.00522

[9] Männistö T, Vääräsmäki M, Pouta A, et al. (2010). Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in

later life. The Journal of clinical endocrinology and metabolism, 95(3), 1084–1094. https://doi.org/10.1210/jc.2009-1904

[10] Männistö T, Vääräsmäki M, Pouta A, et al. (2009). Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. The Journal of clinical endocrinology and metabolism, 94(3), 772–779. https://doi.org/10.1210/jc.2008-1520

[11] Sahu MT, Das V, Mittal S, et al. (2010). Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. Archives of gynecology and obstetrics, 281(2), 215–220. https://doi.org/10.1007/s00404-009-1105-1

[12] Cleary-Goldman J, Malone FD, Lambert-Messerlian G, et al. (2008). Maternal thyroid hypofunction and pregnancy outcome. Obstetrics and gynecology, 112(1), 85–92. https://doi.org/10.1097/AOG.0b013e3181788dd7

[13] Alexander EK, Pearce EN, Brent GA, et al. (2017). 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid : official journal of the American Thyroid Association, 27(3), 315–389. https://doi.org/10.1089/thy.2016.0457

[14] De Groot L, Abalovich M, Alexander EK, et al. (2012). Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. The Journal of clinical endocrinology and metabolism, 97(8), 2543–2565. https://doi.org/10.1210/jc.2011-2803

[15] Shan, Z., & Teng, W. (2019). Thyroid hormone therapy of hypothyroidism in pregnancy. Endocrine, 66(1), 35–42. https://doi.org/10.1007/s12020-019-02044-2

[16] Maraka S, Ospina NM, O'Keeffe DT, et al. (2016). Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid : official journal of the American Thyroid Association, 26(4), 580–590. https://doi.org/10.1089/thy.2015.0418

[17] Dash SC, Sahoo N, Rout U, et al. (2022). Outcomes With Levothyroxine Treatment in Early Pregnancy With Subclinical Hypothyroidism. Cureus, 14(5), e24984.

https://doi.org/10.7759/cureus.24984

[18] Taylor PN, Albrecht D, Scholz A, et al. (2018). Global epidemiology of hyperthyroidism and hypothyroidism. Nature reviews. Endocrinology, 14(5), 301–316. https://doi.org/10.1038/nrendo.2018.18

[19] Taylor PN, Albrecht D, Scholz A, et al. (2018). Global epidemiology of hyperthyroidism and hypothyroidism. Nature reviews. Endocrinology, 14(5), 301–316. https://doi.org/10.1038/nrendo.2018.18

[20] Guidelines for the management of thyroid disorders in pregnancy and the postpartum period (2nd ed.)[J]. Chinese Journal of Endocrinology and Metabolism,2019(08):636-665.

[21] Cao Zeyi. Chinese Obstetrics and Gynecology [M]. Beijing: People's Health Publishing House, 2008

[22] Han, Y., Wang, J., Wang, X, et al. (2022). Relationship Between Subclinical Hypothyroidism in Pregnancy and Hypertensive Disorder of Pregnancy: A Systematic Review and Meta-Analysis. Frontiers in endocrinology, 13, 823710. https://doi.org/10.3389/fendo.2022.823710

[23] Fletcher A K, Weetman. (1998). Hypertension and hypothyroidism. Journal of human hypertension, 12(2), 79–82. https://doi.org/10.1038/sj.jhh.1000574

[24] Danzi S, Klein I. (2012). Thyroid hormone and the cardiovascular system. The Medical clinics of North America, 96(2), 257–268. https://doi.org/10.1016/j.mcna.2012.01.006

[25] Sheffield J S, Cunningham F G. (2004). Thyrotoxicosis and heart failure that complicate pregnancy. American journal of obstetrics and gynecology, 190(1), 211–217. https://doi.org/10.1016/s0002-9378(03)00944-x

[26] Danzi S, Klein I. (2003). Thyroid hormone and blood pressure regulation. Current hypertension reports, 5(6), 513–520. https://doi.org/10.1007/s11906-003-0060-7

[27] Rodondi N, Newman AB, Vittinghoff E, et al. (2005). Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Archives of internal medicine, 165(21), 2460–2466. https://doi.org/10.1001/archinte.165.21.2460

[28] Taddei S, Caraccio N, Virdis A, et al. (2003). Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. The Journal of clinical endocrinology and metabolism, 88(8), 3731–3737. https://doi.org/10.1210/jc.2003-030039

[29] Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth, Korevaar TIM., Derakhshan A, Taylor P N, et al. (2019). Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity With Preterm Birth: A Systematic Review and Meta-analysis. JAMA, 322(7), 632–641. https://doi.org/10.1001/jama.2019.10931

[30] WANG Xia, CHEN Hong-bo, WANG Pei-ru, LI Lei, ZHANG You-jun. Study on the levels of TSH and FT4 in different gestational weeks of normal pregnancy[J]. Journal of Bengbu Medical College, 2023, 48(3): 327-330. doi: 10.13898/j.cnki.issn.1000-2200.2023.03.011

Table 1(on next page)

Table 1 Basic characteristics of pregnant women

c

Table 1 Basic characteristics of pregnant women

Characteristic		SCH group n = 266	control group n = 672	*p*
Age	years	29.24 ± 3.74	28.81 ± 3.54	0.102
BMI	kg/m2	21.63 ± 3.74	21.66 ± 2.84	0.111
Education	low	22 (13.40)	79 (12.80)	0.838
	medium	62 (37.80)	249 (40.36)	
	high	80 (48.80)	289 (46.84)	
Smoking	no	233 (87.60)	591 (87.90)	0.882
	yes	33 (12.40)	81 (12.10)	
Alcohol consumption	no	256 (96.20)	657 (97.80)	0.191
	yes	10 (3.80)	15 (2.20)	
Family history of diabetes	no	246 (92.50)	629 (93.6)	0.537
	yes	20 (7.50)	43 (6.40)	
Family income	low	80 (30.1)	222 (33.0)	0.234
	medium	110(41.40)	230 (34.20)	
	high	76 (28.60)	220 (32.70)	
Parity	one	174(65.40)	470 (69.90)	0.347
	two	81 (30.50)	182 (27.10)	
	three	11 (4.10)	20 (3.00)	
Folic acid supplementation	no	21 (7.90)	30 (4.50)	0.112
	pre-pregnancy	105 (39.50)	273 (40.60)	
	first trimester	140 (52.60)	369 (54.90)	
VD supplementation	no	107 (40.20)	269 (40.00)	0.276
	pre-pregnancy	53 (19.90)	107 (15.90)	
	first trimester	106 (39.80)	296 (44.00)	

Note: High school graduation and below is defined as low education, university graduation or above is defined as high education; pregnant women who smoke or are exposed to second-hand smoke for more than fifteen minutes per week are defined as smoking; annual family income below RMB100,000 is defined as low income and above RMB200,000 is defined as high income

Table 2(on next page)

Comparison of pregnancy outcomes between SCH and control groups

Comparison of pregnancy outcomes between SCH and control groups

Table 2 Comparison of pregnancy outcomes between SCH and control groups

Outcomes		SCH group	control group	*p*
Pregnant women		n = 266	n = 672	
GDM	no	230 (86.50)	582 (86.60)	0.954
	yes	36 (13.50)	90 (13.40)	
HDP	no	251 (94.40)	654 (97.30)	0.027
	yes	15 (5.60)	18 (2.70)	
PROM	no	180 (67.70)	501 (74.60)	0.033
	yes	86 (32.30)	171 (25.40)	
Newborn				
V/ASD	no	255 (95.90)	660 (98.20)	0.036
	yes	11 (4.10)	12 (1.80)	
RDS	no	259 (97.40)	665 (99.00)	0.070
	yes	7 (2.60)	7 (1.00)	
PTB	no	255 (95.90)	658 (97.90)	0.079
	yes	11 (4.10)	14 (2.10)	
AWB	low	249 (93.60)	637 (94.80)	0.231
	normal	9 (3.40)	11 (1.60)	
	high	8 (3.00)	24 (3.60)	
Hyperbilirubinemia	no	155 (58.30)	450 (67.00)	0.012
	yes	111 (41.70)	222 (33.00)	
Pneumonia	no	250 (94.00)	657 (97.80)	0.003
	yes	16 (6.0)	15 (2.20)	

Table 3(on next page)

Comparison of pregnancy outcomes between the SCH and non-SCH groups at different stages of pregnancy

Comparison of pregnancy outcomes between the SCH and non-SCH groups at different stages of pregnancy

Table 3 Comparison of pregnancy outcomes between the SCH and non-SCH groups at different stages of pregnancy

First trimester		SCH Group n = 125	non-SCH Group n = 813	*p*
GDM	no	99 (79.20)	713 (87.70)	0.009
	yes	26 (20.80)	100 (12.30)	
HDP	no	113 (90.40)	792 (97.40)	0.001
	yes	12 (9.60)	21 (2.60)	
Pneumonia	no	116 (92.80)	791 (97.30)	0.019
	yes	9 (7.20)	22 (2.70)	
Second trimester		SCH Group n = 77	non-SCH Group n = 861	*p*
HDP	no	71 (92.20)	834 (96.90)	0.046
	yes	6 (7.80)	27 (3.10)	
PTB	no	71 (92.20)	842 (97.80)	0.011
	yes	6 (7.80)	19 (2.20)	
AWB	normal	71 (92.20)	815 (94.70)	0.002
	low	6 (7.80)	14 (1.60)	
	high	0 (0.00)	32 (3.70)	
Hyperbilirubinemia	no	36 (46.80)	569 (66.10)	0.001
	yes	41 (53.20)	292 (33.90)	
RDS	no	73 (94.80)	851 (98.80)	0.021
	yes	4 (5.20)	10 (1.20)	
Third trimester		SCH Group n =119	non-SCH Group n = 819	*p*
PTB	no	111 (93.30)	802 (97.90)	0.008
	yes	8 (6.70)	17 (2.10)	

Table 4(on next page)

A multifactorial logistic regression model of SCH in pregnancy and five pregnancy outcomes

A multifactorial logistic regression model of SCH in pregnancy and five pregnancy outcomes

Table 4 A multifactorial logistic regression model of SCH in pregnancy and five pregnancy outcomes

Outcomes		*p*	OR	95% CI
HDP	Model 1	0.029	2.204	1.083-4.487
	Model 2	0.035	3.201	1.087-9.423
	Model 3	0.066	2.822	0.932-8.543
PROM	Model 1	0.031	1.412	1.032-1.932
	Model 2	0.130	1.378	0.910-2.085
	Model 3	0.137	1.373	0.904-2.086
V/ASD	Model 1	0.030	2.589	1.098-6.105
	Model 2	0.073	2.809	0.910-8.677
	Model 3	0.060	2.989	0.953-9.378
Hyperbilirubinemia	Model 1	0.008	1.486	1.107-1.995
	Model 2	0.001	2.128	1.435-3.154
	Model 3	0.001	2.114	1.421-3.144
Pneumonia	Model 1	0.003	3.018	1.447-6.295
	Model 2	0.003	3.816	1.597-9.119
	Model 3	0.002	3.975	1.655-9.551

Note: Model 1 adjusted for age, BMI, parity, smoking and alcohol consumption, Model 2 added education, family income, family history of diabetes and history of induced abortion to Model 1, and Model 3 added folic acid, VD supplementation and history of SCH to Model 2

Table 5(on next page)

Comparison of pregnancy outcomes between the cured, non-cured and control groups

Comparison of pregnancy outcomes between the cured, non-cured and control groups

Table 5 Comparison of pregnancy outcomes between the cured, non-cured and control groups

Outcomes		control group n=672	cured group n=219	non-cured group n=47	*p*
HDP	no	654 (97.30)[a]	211 (96.30)[a]	40 (85.10)[b]	0.001
	yes	18 (2.70)[a]	8 (3.70)[a]	7 (14.90)[b]	
PROM	no	501 (74.60)[a]	152 (69.40)[ab]	28 (59.60)[b]	0.040
	yes	171 (25.40)[a]	67 (30.60)[ab]	19 (40.40)[b]	
PTB	no	658 (97.90)[a]	214 (97.70)[a]	41 (87.20)[b]	0.002
	yes	14 (2.10)[a]	5 (2.30)[a]	6 (12.80)[b]	
AWB	normal	637 (94.80)[a]	207 (94.50)[a]	42 (89.40)[b]	0.015
	low	11 (1.60)[a]	4 (1.80)[a]	5 (10.60)[b]	
	high	24 (3.60)[a]	8 (3.70)[a]	0 (0.00)[b]	
Hyperbilirubinemia	no	450 (67.00)[a]	133 (60.70)[ab]	22 (46.80)[b]	0.008
	yes	222 (33.00)[a]	86 (39.30)[ab]	25 (53.20)[b]	
V/ASD	no	660 (98.20)[a]	212 (96.80)[ab]	43 (91.50)[b]	0.043
	yes	12 (1.80)[a]	7 (3.20)[ab]	4 (8.50)[b]	
RDS	no	665 (99.0)[a]	215 (98.20)[ab]	44 (93.60)[b]	0.027
	yes	7 (1.00)[a]	4 (1.80)[ab]	3 (6.40)[b]	

Note: The Bonferroni method is used to evaluate α Perform correction, and differences in a and b between groups indicate statistically significant differences

Table 6(on next page)

Results of Spearman's rank correlation of TSH levels in different trimesters

Results of Spearman's rank correlation of TSH levels in different trimesters

Table 6 Results of Spearman's rank correlation of TSH levels in different trimesters

Total population n=938	Gestation Stage	r	*p*
	First and second trimester	0.114	0.001
	First and third trimester	0.086	0.008
	Second and third trimester	0.550	0.001
Control group n=672	First and second trimester	0.179	0.001
	First and third trimester	0.208	0.001
	Second and third trimester	0.573	0.001

Figure 1

Flow chart of participants participation in the study

Flow chart of participants participation in the study

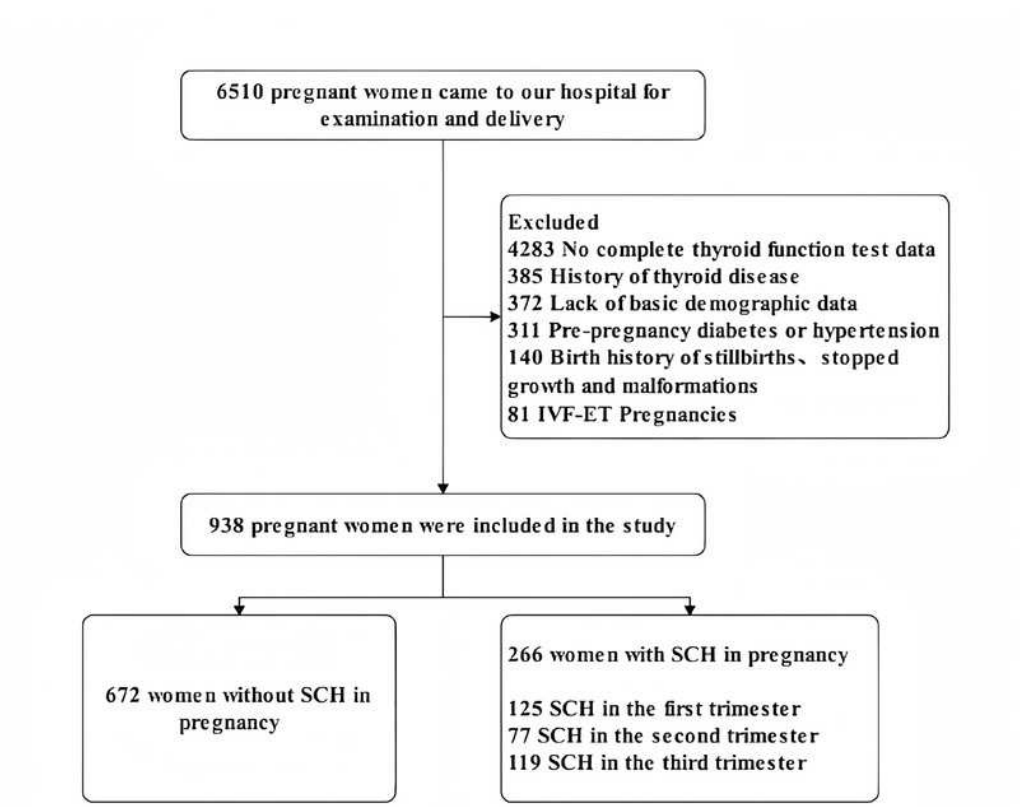

Figure 2

Correlation of TSH levels in the control group across different trimesters

Correlation of TSH levels in the control group across different trimesters