The prevalence of thyroid disorders during early pregnancy in China: the benefits of universal screening in the first trimester of pregnancy


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Running Title: Screening for Thyroid Disease during Early Pregnancy

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Abstract

Context: Maternal thyroid disorders during early pregnancy can influence the pregnancy outcome and the fetal development. The recent Endocrine Society Clinical Practice Guideline recommends a case-finding approach in which pregnant women who are high-risk for developing thyroid disease are tested.

Objective: The purpose of this study was to use first trimester-specific reference intervals of thyroid-related hormones to explore the prevalence of thyroid dysfunction during early pregnancy and to analyze effectiveness of different screening strategies.

Design: This was a multi-center cohort study.

Method: A total of 2,899 pregnant women were enrolled in this study during their first trimester of gestation. Levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), thyroid peroxides antibodies (TPOAb) were measured and thyroid disorders of pregnant women were diagnosed based on the first trimester-specific reference intervals.

Results: The prevalence of hypothyroidism were significantly higher in the high-risk group than in the non-high risk group (10.9% vs. 7.0%, χ²=7.1, P=0.008). The prevalence of hyperthyroidism was no significant difference between the high-risk group and the non-high risk group (2.7% vs. 1.6%, χ²=2.27, P=0.13). Elevated levels of TPOAb and a personal history of thyroid disease increased the risk of thyroid dysfunction.

Conclusions: A case-finding strategy for screening thyroid function in high-risk group would miss about 81.6% pregnant women with hypothyroidism and 80.4% pregnant women with hyperthyroidism.

Keywords: thyroid dysfunction, first trimester pregnancy, screening, risk factor
Introduction

Development of maternal thyroid disorders during early pregnancy can influence the pregnancy outcome and fetal development. Thyroid dysfunction can lead to premature birth, pregnancy-induced hypertension, increased fetal mortality, and low infant birth weight. [1-4] Maternal hypothyroidism and hypothyroxinaemia in the first trimester of pregnancy may be harmful to fetal brain development and lead to mental retardation. [5,6] In view of the potential adverse outcomes associated with maternal thyroid disorders and the obvious benefits of treatment, some expert panels have suggested routine thyroid function screening in all pregnant women. [7,8] However, the Endocrine Society Clinical Practice Guideline [9] recommends a case-finding approach where only women at high-risk for thyroid disorders are tested; these women include those who have a personal or family history of thyroid disease, a personal history of type I diabetes or other autoimmune disorders, clinical signs suggestive of thyroid disorders, goiter, thyroid antibodies, history of previous therapeutic head or neck irradiation, or a history of miscarriage, preterm delivery or infertility. The aim of this study was to use first trimester-specific reference intervals of thyroid-related hormones to determine the prevalence of thyroid dysfunction during early pregnancy and to evaluate efficiency of the case-finding strategy vs. the universal screening strategy.

Materials and Methods

Subjects

Women were recruited from the routine antenatal clinics in ten hospitals from May 2005 through June 2008 in Shenyang, China. Eligibility criteria included pregnant women within
the first 12 weeks of gestation and no history of living in endemic goitre areas. A total of 2,899 pregnant women living in iodine-adequate areas in their first trimester of pregnancy participated. The medical ethics committee of the first affiliated hospital of China Medical University approved this study and all participating women gave informed written consent. Duration of gestation was calculated based on the dates of their last menstrual period and confirmed by ultrasonography. All participants were specifically answered a questionnaire about reproductive histories (miscarriages, preterm deliveries, and infertility), personal and family history of thyroid disorders (including first and second degree relatives), personal history of type I diabetes or other autoimmune diseases, and history of therapeutic head or neck irradiation by the obstetrician of the ten hospitals. Based on Endocrine Society Clinical Practice Guidelines, women with a personal or family history of thyroid disease, a personal history of type I diabetes or other autoimmune disorders, clinical signs suggestive of thyroid disorders, goiter, thyroid antibodies, a history of previous therapeutic head or neck irradiation, a history of miscarriage, preterm delivery and infertility were identified as at high risk for thyroid disease during pregnancy. [9]

Methods of sampling and laboratory testing

Blood samples were obtained from each participant in the morning after overnight fasting. All sera obtained were immediately analyzed for thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), and thyroid peroxidase antibody (TPOAb) concentrations using a chemiluminescence immunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA). The functional sensitivity of the TSH assay was 0.02 mIU/L. The intra-assay coefficients of variation (CV) of serum TSH, FT4, FT3, TPOAb were 1.57%–4.12%, 2.24%–6.33%, 0.57%–4.31%, and
2.42%–5.63%, respectively. The inter-assay CVs were 1.26%–5.76%, 4.53%–8.23%, 3.50%–5.19%,
and 5.23%–8.16%, respectively. Urinary iodine excretion was measured by the colorimetric
cericion–arsenious acidash method, based on the Sandell–Kolthoff reaction. The intra- and inter-assay
CVs were < 7%.

**Trimester-specific reference intervals for TSH, FT3, and FT4 and diagnostic criteria**

The first trimester-specific reference intervals used to diagnose thyroid dysfunctions were based
on those determined previously.[10] The first trimester-specific reference ranges for TSH, FT4, and
FT3 were 0.13–3.93 mIU/L, 12.00–23.34 pM, and 3.46–7.70 pM, respectively. Overt hypothyroidism,
subclinical hypothyroidism, and hypothyroxinemia were defined by the first trimester-specific
reference intervals for TSH, FT3, and FT4 as described previously.[10] Overt hyperthyroidism and
subclinical hyperthyroidism were identified as decreased TSH levels with increased FT3 or FT4 and
with a normal range FT3 or FT4, respectively. A TPOAb concentration ≥ 50 IU/mL was considered
abnormal.

Women, who were found to have thyroid dysfunction or euthyroid women with TPOAb positive
had thyroid function tests at least once during the second and third trimesters. Women with
subclinical hypothyroidism were recommended to receive L-T4 treatment and the drug
dosage was adjusted according to their serum TSH level. Women with clinical
hypothyroidism were offered treatment. Treatment of hyperthyroidism women was based on the
endocrinologist’s clinical judgment and if necessary, antithyroid drug was administrated.
Statistical analysis

Data analysis was performed using SPSS software (version 14.5. SPSS Inc., Cary, NJ, USA). Statistical comparisons were analyzed with the chi-square test. A $P$-value less than or equal to 0.05 was considered to be statistically significant. Based on the results of the chi-square test, statistically significant variables were assessed by multivariate logistic regression analysis.

Results

Characteristics of pregnant women

The average age of the 2,899 women enrolled in the study was 27.61±3.55 years old and median duration of pregnancy at initial analysis was 6 weeks (4-12 weeks). Median urinary iodine of these pregnant women was 177.15 µg/L. Fifty-two women (1.8%) had personal history of thyroid disorders, which included 21 hypothyroidism (overt or subclinical), 11 hyperthyroidism (overt or subclinical), 11 goiter/thyroid nodule, and 9 other thyroid disorders. 179 women (6.0%) had family history of thyroid disorders. Three women (0.1%) had history of other autoimmune diseases. 147 women (5.0%) had history of miscarriage. Three women (0.1%) had history of preterm delivery and five women (0.2%) had history of infertility treatment. None had history of head or neck irradiation. Using the Endocrine Society Clinical Practice guidelines,[9] we classified 367 (12.7%) women, who had a personal or family history of thyroid disease, a personal history of type 1 diabetes or other autoimmune disorders, a history of miscarriage, preterm delivery and infertility, a history of head or neck irradiation, as a high risk. [9] Demographic characteristics of participants are shown in Table 1. There were no significant differences in maternal age, ethnicity, smoking habits, or number of previous pregnancies between the women in the high-risk group and those in the non-high risk group.
Prevalence of thyroid dysfunction in the first trimester of pregnancy and relative risk (RR) analysis

TSH, FT4, FT3 and TPOAb levels were measured in all 2,899 pregnant women. Of the 2,899 women in the study, 294 women had thyroid dysfunction. The prevalence of thyroid dysfunction was 10.2%. The prevalences of hyperthyroidism, hypothyroidism, and hypothyroxinemia were 1.8%, 7.5% and 0.9%, respectively (Table 2). TPOAb was positive in 279 (9.6%) of the 2,899 women. The number of euthyroid with antibodies was 196 (6.8%). The prevalence of thyroid dysfunction in high-risk group was significantly higher than in non-high risk group (15.0% vs. 9.4%, P=0.001, χ²=10.8). The prevalence of thyroid dysfunction in pregnant women with personal history of thyroid diseases (30.8% vs.9.8%, P=0.000), abnormal TPOAb levels (29.7% vs. 8.1%, P=0.000) and personal history of other autoimmune disorders (66.7% vs. 10.1%, P = 0.018) was significantly higher than in pregnant women without risk factors. A logistic multiple regression showed that personal history of thyroid diseases (OR = 2.3, P = 0.016) and positive TPOAb (OR = 4.6, P = 0.000) were risk factors for the increase in thyroid dysfunction.

Prevalence of hypothyroidism, hyperthyroidism, and hypothyroxinemia in the first trimester of pregnancy and RRs analysis

Two hundred seventeen women (7.5%) had elevated TSH levels. Eight of them were diagnosed with overt hypothyroidism. Of the eight women with raised TSH and low FT4, seven had TPOAbs. The prevalence of elevated TSH was higher in the high-risk group than in the non-high risk group.
(10.9% vs. 7.0%, $\chi^2=7.1$, $P=0.008$). The prevalence of hypothyroidism in TPOAb-positive (N=279) and personal history of thyroid disease (N=51) pregnant women was significantly higher than in TPOAb-negative pregnant women (25.8% vs. 5.5%, $P=0.000$) and non-personal history of thyroid disease pregnant women (23.1% vs. 7.2%, $P<0.001$). It was noteworthy that 177 of 217 women with elevated TSH (81.6%) were in the non-high risk group.

Fifty-one women (1.8%) with low TSH levels were diagnosed with overt or subclinical hyperthyroidism. There was no difference in the prevalence of hyperthyroidism between the high-risk group and the non-high risk group (2.7% vs. 1.6%, $\chi^2=2.27$, $P=0.13$). The prevalence of hyperthyroidism in TPOAb-positive (N=279) and personal history of thyroid disease (N=51) pregnant women was significantly higher than in TPOAb-negative pregnant women (4.0% vs. 1.5%, $P=0.007$) and non-personal history of thyroid disease pregnant women (7.7% vs. 1.7%, $P=0.006$). It was noteworthy that only 10 of 51 (19.6%) women with hyperthyroidism belonged to the high-risk group; 41 (80.4%) women with hyperthyroidism were in the non-high risk group.

There was no difference in the prevalence of hypothyroxemia between the high-risk group and the non-high risk group (0.9% vs. 0.9%, $\chi^2=0.008$, $P=0.928$). Figure 1 compares the prevalence of thyroid disorders in the high-risk group and the non-high risk group and figure 2 presents the rates of missed diagnoses if screening were to be performed only in the high-risk population.

A logistic multiple regression was used for risk factor analysis. It showed that positive TPOAb was a risk factor (OR = 5.8, $P = 0.000$) for the increase in hypothyroidism and the presence of TPOAb (OR=2.3, $P=0.022$) and personal history of thyroid diseases (OR=3.6, $P=0.025$) increase the risk of hyperthyroidism.
Discussion

Maternal overt hypothyroidism, subclinical hypothyroidism, and hypothyroxinemia are associated with adverse outcomes in pregnancy, including miscarriage, pregnancy-induced hypertension, preterm delivery, placental abruption, and impaired neuropsychological development of children.\textsuperscript{[1-6]} Haddow et al.\textsuperscript{[5]} and Pop et al.\textsuperscript{[6]} reported that maternal hypothyroidism and hypothyroxinaemia occurring in the first half of pregnancy may be harmful to embryo-fetal brain development and lead to intellectual retardation in the offspring. Our group also found that maternal subclinical hypothyroidism, hypothyroxinaemia, and euthyroidism with elevated TPOAb titers were all statistically significant predictors of lower motor and intellectual development at 25-30 months.\textsuperscript{[11]} In Haddow’s report the IQ scores of children whose mothers with hypothyroidism were treated during pregnancy were similar to those of the control children of mothers with normal thyroid function during pregnancy.\textsuperscript{[5]} Berbel et al. reported that a delay of 6–10 weeks in iodine supplementation of hypothyroxinemic mothers at the beginning of gestation in an area of mild iodine deficiency increases the risk of neurobehavioral performance delay in their offsprings.\textsuperscript{[12]}

Maternal thyroid function is of great importance for the fetus during the first trimester of pregnancy. Stricker et al.\textsuperscript{[13]} reported that 3.6% of patients with elevated TSH would be missed and 3.7% of patients with low TSH level would be misdiagnosed as having a lower TSH level by using the non-pregnant reference intervals to diagnose thyroid diseases. Vaidya et al.\textsuperscript{[14]} concluded that the prevalence of hypothyroxemia increased 3.7% when first trimester-specific reference ranges were used rather general population reference intervals. Our group used two different series of reference intervals to calculate the prevalence of thyroid hormone deficiency and also found that 2% patients with subclinical hypothyroidism would be misclassified if general population reference intervals were
These results indicate that first trimester-specific reference ranges must be used to evaluate thyroid function in pregnancy.

In the present study we evaluated the prevalence of thyroid dysfunction by screening 2,899 pregnant women using the first trimester-specific reference intervals from our previous work. The results showed that high-risk women, classified based on Endocrine Society Clinical Practice Guidelines, had more than a 1.5-fold increased risk of hypothyroidism (subclinical or overt) and a 1.7-fold increased risk of hyperthyroidism (subclinical or overt) during early pregnancy than did women in the non-high risk group. However, screening for thyroid diseases only in the high-risk pregnant women, as the guidelines recommend, would have meant that about 81.6% women with hypothyroidism, (2.7% with overt hypothyroidism and 78.8% with subclinical hypothyroidism) and 80.4% women with hyperthyroidism (41.2% with overt hyperthyroidism and 39.2% with subclinical hyperthyroidism) would be missed. Our results were similar to those reported by Vaidya et al., who concluded that targeted thyroid function testing of only high-risk pregnant women would miss nearly one third of women with overt/subclinical hypothyroidism during early pregnancy by using non-pregnant population reference intervals. A higher percentage of missed diagnosis in our study than Vaidya’s maybe because Vaidya defined euthyroidism in that study as a TSH less than 4.2, whereas the present study defined euthyroidism as a TSH less than 3.93. Recently another study of Negro reached similar conclusions. In this study, they randomized pregnant women in the first trimester to either universal screening group or case-finding group. They showed that the case-finding approach fails to detect the majority of pregnant women with thyroid dysfunction. The benefits and risks of universal testing or case finding strategies in pregnant women are debated. As Brent et al. previously pointed out, the potential adverse outcomes are so significant and the tools to
diagnose and treat thyroid disease are easily accessible, it is no longer acceptable even one third of pregnant women to remain undiagnosed. Our results support performing universal screening early in pregnancy for thyroid disorders using the first trimester-specific reference intervals. In 2008, Dosiou et al.\textsuperscript{[20]} reported that screening pregnant women for TSH concentrations in the first trimester of pregnancy was cost-saving compared with no screening and screening using anti-TPO antibodies was also economically favorable. The study of Thung SF used marginal cost per quality-adjusted life year (QALY) as the main outcome measure and shown that universal screening for subclinical hypothyroidism in pregnancy would be a cost-effective strategy\textsuperscript{[21]}. Regarding the main argument against the universal screening has been the lack of clinical trial evidence showing that treatment in maternal mild hypothyroidism prevents neuropsychological deficit in children and other obstetric complications that more randomized trials are needed.

The most appropriate screening test for thyroid dysfunction in early pregnancy is still uncertain. Most would advocated using TSH as the initial screening test, because TSH is a more sensitive marker of thyroid status than FT4 and it reflects the physiologic log/linear relationship of TSH to FT4\textsuperscript{[22-23]}. TPOAb measurement should also be considered due to the relation with adverse pregnancy events, such as postpartum thyroiditis, recurrent miscarriage, and postpartum depression. In addition, 20-30\% of women with postpartum thyroiditis develop permanent hypothyroidism\textsuperscript{[24-25]} Negro et al. reported that treatment of euthyroid pregnant women who were positive for TPOAb with levothyroxine lowered the chance of miscarriage and premature delivery. Selenium supplementation during pregnancy and in the postpartum period also reduces thyroid inflammatory activity and the incidence of postpartum thyroid dysfunction and hypothyroidism\textsuperscript{[26-27]}. Maternal hypothyroxinaemia during pregnancy may affect neuropsychological development of offspring\textsuperscript{[6,11,12]}, which affected 0.9\%
of the cohort of our study with equal frequency in the high-risk and non-high risk groups, is identified only if serum TSH is measured. Therefore, we support using TSH, FT4, and TPOAb as the initial screening test for thyroid dysfunction in early pregnancy.

In conclusion, our study confirms that a case-finding strategy for screening thyroid function would miss about 81.6% pregnant women with hypothyroidism and 80.4% pregnant women with hyperthyroidism.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

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References


17. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Colin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease:
scientific review and guidelines for diagnosis and management. JAMA 2004 291:228–238


Figure 1. Comparison of the prevalence of thyroid disorders in the high-risk group and the non-high risk group.

Figure 2. The rates of missed diagnoses if screening were to be performed only in the high-risk population.
TABLE 1. Demographic characteristics of pregnant women.

<table>
<thead>
<tr>
<th>Demographic characteristics (N=2899)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean maternal age (yr) ( x ± s )</strong></td>
</tr>
<tr>
<td><strong>Median (range) gestational age at screening (weeks)</strong></td>
</tr>
<tr>
<td><strong>Median urinary iodine (µg/L)</strong></td>
</tr>
<tr>
<td><strong>Number of previous pregnancies, n (%)</strong></td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>One</td>
</tr>
<tr>
<td>Two</td>
</tr>
<tr>
<td>Three or more</td>
</tr>
<tr>
<td><strong>History of fertility treatment, n (%)</strong></td>
</tr>
<tr>
<td><strong>History of miscarriages, n (%)</strong></td>
</tr>
<tr>
<td><strong>History of preterm delivery, n (%)</strong></td>
</tr>
<tr>
<td><strong>History of smoking, n (%)</strong></td>
</tr>
<tr>
<td><strong>Personal history of thyroid disease, n (%)</strong></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Goiter/nodule</td>
</tr>
<tr>
<td>Other thyroid disease</td>
</tr>
<tr>
<td><strong>History of head or neck irradiation, n (%)</strong></td>
</tr>
<tr>
<td><strong>Family history of thyroid disease, n (%)</strong></td>
</tr>
<tr>
<td><strong>Type 1 diabetes/autoimmune disease a, n (%)</strong></td>
</tr>
</tbody>
</table>

a Including rheumatoid arthritis (n=3)
# TABLE 2. The prevalence of thyroid disorders during early pregnancy based on various characteristics.

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>N</th>
<th>Low TSH</th>
<th>Elevated TSH</th>
<th>Normal TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High FT4</td>
<td>Normal FT4</td>
<td>Total</td>
</tr>
<tr>
<td>All women</td>
<td>2899</td>
<td>28 (1.0)</td>
<td>23 (0.8)</td>
<td>51 (1.8)</td>
</tr>
<tr>
<td>High-risk group</td>
<td>367</td>
<td>7 (1.9)</td>
<td>3 (0.8)</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>Non-high risk group</td>
<td>2532</td>
<td>21 (0.8)</td>
<td>20 (0.8)</td>
<td>41 (1.6)</td>
</tr>
<tr>
<td>TPOAb positive</td>
<td>279</td>
<td>7 (2.5)</td>
<td>4 (1.5)</td>
<td>11 (4.0)</td>
</tr>
<tr>
<td>History of thyroid disorder</td>
<td>52</td>
<td>4 (7.7)</td>
<td>0</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Family history of thyroid disease</td>
<td>179</td>
<td>3 (1.7)</td>
<td>3 (1.7)</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td>History of other autoimmune diseases</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>History of miscarriages</td>
<td>147</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>History of preterm delivery</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>History of fertility treatment</td>
<td>5</td>
<td>1 (20)</td>
<td>0</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

Data are expressed as number of pregnant women with percent of total in parentheses.
## TABLE 3. RRs for hypothyroidism and hyperthyroidism at screening.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>TPOAb positive</td>
<td>5.8</td>
<td>4.2-8.1</td>
</tr>
<tr>
<td>Personal history of thyroid disorder</td>
<td>2.0</td>
<td>1.0-4.2</td>
</tr>
<tr>
<td>Family history of thyroid disorders</td>
<td>1.0</td>
<td>0.6-1.8</td>
</tr>
<tr>
<td>Personal history of other autoimmune disorders</td>
<td>3.5</td>
<td>0.3-44.6</td>
</tr>
<tr>
<td>History of miscarriage</td>
<td>1.2</td>
<td>0.7-2.2</td>
</tr>
<tr>
<td>History of preterm delivery</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>History of fertility treatment</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Figure 1. Comparison of the prevalence of thyroid disorders in the high-risk group and the non-high risk group.
Figure 2. The rates of missed diagnoses if screening were to be performed only in the high-risk population.