Thyroid Function Status and Its Impact on Feto-maternal Outcome in Pregnant Women in Bangladesh: A Hospital-based Cross-sectional Study

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Abstract

Background: Thyroid disorders are common in pregnancy and are associated with adverse pregnancy outcomes. The objective of the present study was to assess thyroid status and its association with adverse maternal and neonatal outcomes in pregnant women in Bangladesh.

Methods: This cross-sectional study was conducted on 252 women with term pregnancy included from the Department of Gynecology and Obstetrics of Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital from September 2019 to October 2020. Their baseline information was collected by face-to-face interviews using a semi-structured questionnaire and approximately 3 ml of blood was drawn after maintaining all aseptic precautions for FT4, TSH, and anti-thyroid antibody (anti-TPO-Ab and anti-TG-Ab) estimation. All laboratory procedures were performed using an autoanalyzer (ADVIA Centaur CP, manufactured by Siemens Healthcare Diagnostic Inc., USA). To assess the thyroid function status of the newborn, blood was drawn by the heel-prick technique, and TSH was analyzed using the same autoanalyzer.

Results: The mean gestational age of the pregnant women was 38.3 (SD 1.3) weeks. Their mean FT4 and TSH levels were 0.96 (SD 0.1) ng/dL (reference range 0.87–1.54 ng/dL for pregnant women) and 1.8 (SD 1.6) mIU/ml (reference range 0.3–3 mIU/L for pregnant women), respectively. The prevalence of overt hypothyroidism was 3.2%, and subclinical hypothyroidism was 5.2%. None of the pregnant women were diagnosed with overt or subclinical hyperthyroidism. All the women with overt hypothyroidism and almost half of the patients with subclinical hypothyroidism had a positive anti-thyroid antibody status (overall prevalence of positive anti-thyroid antibody was 13%). Adverse maternal and fetal outcomes, such as postpartum hemorrhage, low birth weight, intrauterine growth retardation and neonatal hypothyroidism, were more prevalent among women with overt or subclinical hypothyroidism (p value <0.001).

Conclusion: A substantial number of pregnant women in Bangladesh suffer from subclinical or overt hypothyroidism, which increases their risk of adverse pregnancy outcomes.

Keywords: Thyroid function, Hypothyroidism, Hyperthyroidism, TSH, Pregnancy

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Introduction

Thyroid disorders, particularly clinical or subclinical hypothyroidism, are common in pregnant women [1,2]. The physiological and hormonal stress of pregnancy results in increased production of thyroid hormones such as thyroxin (T4) and tri-iodothyronine (T3). During early pregnancy, β-HCG, a hormone homologous to thyroid stimulating hormone (TSH), stimulates this elevated production of thyroid hormones. Simultaneously, estrogen-mediated overproduction of thyroid binding globulin (TBG), which has a high affinity for T4, leads to lowered free T4 concentrations in serum. This low T4 level further stimulates the pituitary gland to secrete TSH and subsequently increase thyroid hormone secretion. The net effect develops a new equilibrium between free and bound thyroid hormones and therefore a substantial increase in total T4 and T3 levels in the presence of elevated TSH levels, which increases the risk of subclinical hypothyroidism in pregnant women [3-4]. In women with iodine deficiency, their low iodine reserve cannot keep pace with the elevated requirement of iodine for the production of thyroid hormones, which makes them vulnerable to overt hypothyroidism [5]. Hence, hypothyroidism is the most common thyroid disorder in pregnancy, affecting almost 3 to 5% of pregnant women [6]. In developing countries, the burden is much higher than the global burden. For example, in India, more than 11% of pregnant women suffer from hypothyroidism [7], and in Bangladesh, it ranges from 11 to 22% [8]. The high prevalence of iodine deficiency might contribute to this burden of thyroid disorder in this region. More than half of the pregnant women in Bangladesh do not have adequate iodine reserves to meet the requirements during pregnancy [9].

Thyroid disorders, especially hypothyroidism, have a profound impact on maternal and neonatal outcomes of pregnancy. Thyroid hormone has a crucial role in brain development in the developing fetus. Children of hypothyroid mothers have an increased risk of cognitive, neurological and developmental abnormalities if the condition is not recognized and treated promptly [10]. In addition, these children are vulnerable to preterm birth, neonatal respiratory distress syndrome, low birth weight, perinatal morbidity and mortality [11-13]. Maternal adverse events from thyroid disorders include early abortion, gestational hypertension disorders, placental abruption, preterm delivery, increased rate of cesarean section, and postpartum hemorrhage [14].

Considering the high burden of thyroid disorders in pregnant women and its associated risk of adverse maternal and fetal outcomes in developing countries such as Bangladesh, it is crucial to identify women at risk of these adverse outcomes at an early stage. The present study aims to determine the prevalence of thyroid disorders in pregnancy and its maternal and fetal outcomes in a tertiary care hospital in Bangladesh.

Methods

Study design and setting

The present study was a cross-sectional observational study conducted in the Department of Gynecology and Obstetrics of Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital from September 2019 to October 2020.

Participants

Both primigravid and multigravid women with term pregnancy (37 weeks of pregnancy) admitted to the Department of Gynecology and Obstetrics of BSMMU for delivery were considered the study population. The sample size for the present study was determined by using the following formula: \( n = \frac{z^2 \times pq}{d^2} \), where \( p \) = proportion or percentage of prevalence = 22\%, \( q = (1-p) = 78\% \), \( z = \) value of standard normal distribution (\( z \) distribution) at a given level of significance or a given confidence level (1.96 at level of 95% confidence which is constant), and \( d = \) margin of error over the prevalence (5\%). The calculated sample size was 263. However, after exclusion of incomplete data, a total of 252 women were included in the final analysis.

The convenience sampling method was used to recruit the samples. Term pregnant mothers admitted to the selected department, including both primigravida and multigravida, were recruited. Women with toxemia of pregnancy or other acute emergency conditions were excluded from the study.

Data collection procedure

All term pregnant women selected for the study were approached for informed written consent. Then, data were collected from those who provided consent by face-to-face interviews using a semistructured questionnaire. Clinical evaluations, including measurements of height, weight and blood pressure, were taken by calibrated instruments, and thyroid gland examination was performed for every participant. Approximately 3 ml of blood was drawn after maintaining all aseptic precautions for FT4, TSH and anti-thyroid antibody (anti TPO-Ab and anti TG-Ab) estimation. The collected blood was kept at room temperature to clot and centrifuged for 15 minutes at 3000 rpm to obtain serum. The serum of each patient was transferred to two Eppendorf tubes after labelling and stored at -20°C until assay. All assays were performed using an autoanalyzer (ADVIA Centaur CP, manufactured by Siemens Healthcare Diagnostic Inc., USA). According to the thyroid function tests, the studied subjects were divided into groups: euthyroid mothers and mothers with thyroid dysfunction according to American Thyroid Association (ATA) criteria. Pregnancy outcomes were evaluated. To assess the thyroid function status of the newborn, the neonates were assessed clinically for any congenital anomalies. Screening was performed by using special filter paper. Blood was drawn by the heel-prick technique, and
blood samples were collected on special filter paper within 2-5 days of birth. After collection and proper drying, the samples were kept in the envelope, and TSH was analysed using an autoanalyzer (ADVIA Centaur CP, manufactured by Siemens Healthcare Diagnostic Inc., USA).

Operational definitions
For pregnant women, thyroid dysfunction was defined on the basis of cut-off values for TSH set by American Thyroid Association (ATA) guidelines[13]. Thus, functional status was considered normal: TSH < 0.3-3.0 mIU/L (third trimester), FT4 0.8-1.8 ng/dL; hypothyroidism: TSH above 2.50 mIU/L in conjunction with a decreased FT4 less than 0.8 ng/dL or TSH ≥ 10.0 irrespective of their FT4 level; subclinical hypothyroidism: TSH between 2.5-10.0 mIU/L with a normal FT4 0.8-1.8 ng/dL; hyperthyroidism: TSH < 0.10 mIU/L and elevated FT4 above 1.8 ng/dL; subclinical hyperthyroidism: suppressed serum TSH < 0.10 mIU/L with normal FT4 (0.8-1.8 ng/dL); and anti-thyroid antibody: anti-TPO (anti-thyroid peroxidase) ≥ 35 IU/ml or positive anti-TG (anti-thyroglobulin) ≥ 40 IU/ml or positive. Thyroid dysfunction in neonates was defined on the basis of cut-off values for TSH set by operational definitions.

Statistical analysis
Data from the study were analysed using computer-based SPSS (version 25). All continuous variables were expressed as the mean ± SD, and categorical variables are expressed as frequencies or percentages. Variables were compared among functional groups. For comparison of variables, the chi-square test or Fisher’s exact test for categorical variables and independent t test for continuous variables were used as appropriate. Functional status and antibody status were dichotomized on the basis of respective reference values as normal and aberrant/positive. The level of significance was expressed as a p value ≤ 0.05.

Results
The average age of the pregnant women included in the present study was 26.8 (SD 5.5) years. Almost two-thirds of them (65%) were housewives, 24% were service holders and 11% were manual laborers. Almost 70% of the women were from urban areas. The average BMI of the included pregnant women was 25.6 (SD 1.4) kg/m². Their average gestational age was 38.3 (SD 1.3) weeks, and 37% of them were primigravida (Table 1).

The mean FT4 level in the pregnant women was 0.96 (SD 0.1) ng/dL, and the mean TSH level was 1.8 (SD 1.6) mIU/ml. According to the FT4 and TSH cut-off levels, a total of 8 women were suffering from overt hypothyroidism (prevalence 3.2%), and 13 women were suffering from subclinical hypothyroidism (prevalence 5.2%). None of the pregnant women were diagnosed with overt or subclinical hyperthyroidism on biochemical testing in this study who were not previously diagnosed with the condition. A total of 33 women (13%) were positive for anti-thyroid antibodies (Table 2).

Table 3: Thyroid function status according to anti-thyroid antibody status of the pregnant women (This table has no relevance in the manuscript)
Adverse maternal and fetal outcomes were more prevalent among women with overt hypothyroidism compared to euthyroid patients as described in Table 4. For example, postpartum hemorrhage, low birth weight, intrauterine growth retardation and neonatal hypothyroidism were present in 12.5%, 25%, 12.5% and 25% pregnant women with overt hypothyroidism, respectively. Similarly, the prevalence of these adverse events were 7.7% (postpartum hemorrhage), 15% (low birth weight), and 7.7% (intrauterine growth retardation) in women with subclinical hypothyroidism (Table 4).

### Discussion

Thyroid disorder is one of the most common endocrine disorders in women of reproductive age, especially during pregnancy. These disorders have a debilitating impact on maternal and neonatal outcomes of pregnancy. In this context, the present study provides an overview of the prevalence of thyroid disorders and their impact on pregnancy outcomes among pregnant women in this country.

The mean value of FT4 level was 0.96 ng/dL and mean TSH level was 1.8 mIU/ml in the pregnant women included in our study. Similarly, in a recent study, the average TSH level was reported to be 2.74 mIU/L in pregnant women in Bangladesh. However, in that study, a large number of women were diagnosed with hypothyroidism, which might cause the relative high average level of serum TSH[8]. The current guidelines advise using the reference range of TSH based on the results for the particular population and laboratory technique of the Institute[13]. However, there is a lack of evidence on the reference value of TSH in women in Bangladesh. We used a TSH level of 0.3-3 mIU/L as a reference value for the normal range in our pregnant women in the third trimester, which was also used in a previous study for pregnant women of this geographical location[8]. According to this cut-off value, a total of 8.4% of the pregnant women included in our study were diagnosed with hypothyroidism (prevalence of subclinical hypothyroidism 5.2% and overt hypothyroidism 3.2%).

However, none of the women were diagnosed with hyperthyroidism in our study. Few studies are available reporting the prevalence of thyroid disorders during pregnancy among Bangladeshi women. However, hypothyroidism was more common than other thyroid disorders, such as hyperthyroidism. A previous study conducted by Ferdousi et al. stated that the prevalence of hypothyroidism in pregnant women in Bangladesh was 11%, which corroborates our findings[3]. In another study, the prevalence rates of subclinical and overt hypothyroidism and subclinical hyperthyroidism were 17%, 12% and 4%, respectively, which were higher than those in our study[8]. In neighboring India, almost 5.6% of pregnant women suffer from subclinical hypothyroidism, while almost 3.5% suffer from overt hypothyroidism, and 1.5% suffer from subclinical hyperthyroidism[8]. However, the global prevalence of thyroid disorders in pregnancy is lower than that in developing countries, affecting almost 3 to 5% of pregnant women[4]. Anti-thyroid antibody was present in almost 13% of our pregnant women, which corroborates previous studies from both Bangladesh and India[3,4].

In our study, almost 13% of the pregnant women were positive for anti-thyroid antibodies. We found that all the women with overt hypothyroidism and almost half of the patients with subclinical hypothyroidism had a positive anti-thyroid antibody status. Similar finding was reported in a previous study too, where a significant number of pregnant women had a positive anti-thyroid antibodies[39]. However, that study did not find any association between neonatal outcome and positive anti-thyroid antibody status.

A number of reproduction and pregnancy-related factors are associated with thyroid disorders. Thyroid dysfunction increases the risk of infertility resulting from anovulatory cycles, luteal phase defects, high prolactin levels, and sex hormone imbalances in women[69]. In addition, thyroid autoimmunity is associated with recurrent miscarriage, likely due to generalized activation of the immune system and transplacental transfer of antibodies[71].

### Table 4: Pregnancy outcome according to thyroid status

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients with thyroid dysfunction n=21</th>
<th>Euthyroid patients n=231</th>
<th>Total n=252</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism (n=8)</td>
<td>1(12.50)</td>
<td>1(7.69)</td>
<td>3(1.29)</td>
<td>(1.90)</td>
</tr>
<tr>
<td>Subclinical hypothyroidism (n=13)</td>
<td>2(25.00)</td>
<td>2(15.38)</td>
<td>5(2.16)</td>
<td>(3.57)</td>
</tr>
<tr>
<td>Post-purtum hemorrhage</td>
<td>1(12.50)</td>
<td>1(7.69)</td>
<td>2(0.86)</td>
<td>(1.58)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1(25.00)</td>
<td>2(25.00)</td>
<td>3(1.29)</td>
<td>(1.90)</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>2(25.00)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
<td></td>
</tr>
<tr>
<td>Neonatal hypothyroidism (TSH&gt;20 mIU/L)</td>
<td>2(25.00)</td>
<td>0(0.00)</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Hypothyroidism may result in contraction of vascular smooth muscle both in systemic and renal vessels, leading to increased diastolic pressure and peripheral vascular resistance, which increase the risk of hypertensive disorders of pregnancy, such as preeclampsia and eclampsia[18,19].

The findings from the present study emphasize that the estimation and diagnosis of thyroid parameters in pregnant women have significant clinical relevance. However, the study has several limitations. Although in our study we included and evaluated thyroid function in the third trimester of pregnancy, first trimester values are more important than the second and third trimesters, as they have an immense role in maternal and fetal complications later on[1]. If hypothyroidism could be diagnosed at an early stage of pregnancy, treatment with levo-thyroxin would prevent complications[6,10]. Moreover, we used the reference value of TSH levels according to American guidelines due to a lack of local evidence, although it is recommended to use population-level reference values. Furthermore, our study was based on a small sample of pregnant women from a single tertiary care center, which might limit the generalizability of the study findings.

Conclusions

Our study demonstrated that a substantial proportion of pregnant women in Bangladesh suffer from subclinical or overt hypothyroidism, which is associated with adverse maternal and neonatal pregnancy outcomes such as postpartum hemorrhage, low birth weight, intrauterine growth retardation and neonatal hypothyroidism. Hence, early screening and detection of thyroid disorders in pregnant women has clinical significance to prevent these adverse pregnancy outcomes.

Abbreviations:

ATA American Thyroid Association
BSMMU Bangabandhu Sheikh Mujib Medical University
SD Standard deviation
SPSS Statistical Package for the Social Sciences
T3 tri-iodothyronine
T4 thyroxin
TBG thyroid binding globulin
TSH thyroid stimulating hormone

Declarations:

Ethics approval: The study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University. Informed signed consent was obtained from all eligible participants who agreed to participate. The authors declare that the procedures followed the regulations established by the Helsinki Declaration of the World Medical Association.

References

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