The effect of hyperthyroidism in the first trimester of pregnancy on low birth weight

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ABSTRACT

Aim: The diagnosis of thyrotoxicosis in the first trimester of pregnancy is peculiar due to the physiological changes that occur due to pregnancy. There are maternal and fetal adverse effects of hyperthyroidism on pregnancy. In this study, we aimed to evaluate the effect of thyrotoxicosis on newborn weight in pregnant women with gestational transient thyrotoxicosis or Graves' disease who were referred for thyrotoxicosis in the first trimester.

Material and Method: Ninety-four pregnant women in the first trimester with subclinical or overt hyperthyroidism caused by gestational transient thyrotoxicosis or Graves' disease and 30 healthy pregnant women in the same trimester were included in the study. The birth weights of their babies were compared.

Results: Ninety of the patients reached delivery, and four with gestational transient thyrotoxicosis had abortus due to obstetric reasons. No statistical difference was found in terms of the birth weights of the babies in the comparison between the gestational transient thyrotoxicosis, Graves' disease, and the control groups (p>0.05).

Conclusion: In our study, neither gestational transient thyrotoxicosis nor Graves' disease was found to be associated with low birth weight. But since it is known that overt hyperthyroidism may be associated with low birth weight, pregnant women with hyperthyroidism should be followed carefully.

Keywords: Pregnancy complications, first trimester, hyperthyroidism, thyrotoxicosis, low birth weight

INTRODUCTION

Thyroid function tests are increasingly requested in pregnant women by physicians. In the interpretation of test results, the rate of referring patients to internal medicine and endocrinology specialists by family physicians and obstetricians who follow pregnant women is increasing day by day. With early and accurate diagnosis, potential adverse maternal and fetal complications caused by thyroid diseases can be reduced.

The frequency of hyperthyroidism in pregnancy is 0.1-3% (1). The diagnosis of thyrotoxicosis in the first trimester of pregnancy is peculiar due to the physiological changes that occur during pregnancy. Symptoms such as emotional lability, heat intolerance, sweating, and palpitations can also be seen in a normal healthy pregnancy. Symptoms such as tremors and weight loss without loss of appetite are significant in terms of overt hyperthyroidism. In overt hyperthyroidism, low thyrotropin (TSH) is accompanied by increased free thyroxine (fT4) and/or free triiodothyronine (fT3), whereas, in subclinical hyperthyroidism, TSH is low, but the fT3 and fT4 levels are within trimester-specific reference ranges or total triiodothyronine (tT3) and total thyroxine (tT4) are increased less than 1.5 times the normal reference range (2). The increase in thyroid hormone binding globulin (TBG) is responsible for the high tT3 and tT4 levels observed during pregnancy. Because of this physiological increase, an increase of up to 1.5 times the normal reference range for tT3 or tT4 is considered normal in the definition of subclinical hyperthyroidism. On the other hand, the beta subunit of human chorionic gonadotropin (hCG), which starts to increase after fertilization and peaks at the 10-12th gestational week, is similar to TSH and increases thyroid hormone synthesis, and causes suppression of TSH by feedback inhibition. Therefore, trimester-specific TSH reference ranges are recommended for the evaluation of thyroid functions during pregnancy (3).

Gestational thyrotoxicosis, hyperemesis gravidarum, and Graves’ disease should be excluded first in the differential diagnosis of thyrotoxicosis occurring during pregnancy. In addition to these, other etiological causes of hyperthyroidism can be counted as toxic multinodular goiter, toxic adenoma, thyroiditis, exogenous thyroid hormone use, and gestational trophoblastic diseases. Gestational transient thyrotoxicosis...
GTT is a kind of biochemical hyperthyroidism that occurs with an increase in hCG concentrations in the first trimester of pregnancy, without symptoms of thyrotoxicosis. It tends to resolve spontaneously with the normal course of pregnancy and usually does not require antithyroid therapy (ATT). Beta-blockers can be used as needed. Since hCG concentrations are higher in hyperemesis gravidarum and multiple pregnancies, overt hyperthyroidism may be seen with more severe suppression of TSH (4,5).

An enlarged thyroid gland, a pulse rate over 120/min, presence of ophthalmopathy, and a high fT3/fT4 ratio in a pregnant woman with thyrotoxicosis symptoms and overt hyperthyroidism, suggest Graves’ disease. Decreased thyroid blood flow in Doppler ultrasonography is significant for thyroiditis, and increased vascularity is significant for Graves’ disease. Thyrotropin receptor antibodies (TRAbs) help differentiate Graves’ disease from GTT. Since TRAb can cross the placenta, neonatal hyper- or hypothyroidism may occur, therefore it is useful to evaluate TRAb in terms of predicting the fetal prognosis (6). Scintigraphic studies are contraindicated in pregnancy because of the poor pregnancy outcomes associated with radioactive exposure, as well as the risk of fetal hypothyroidism.

After the etiology is of hyperthyroidism determined in a pregnant woman, it should be decided whether treatment will be given according to the underlying cause and appropriate follow-ups should be planned. Propylthiouracil is the treatment of choice in the first trimester when ATT is needed, and the duration of treatment should be kept as short as possible. Since ATT options can cross the placenta, they may cause poor outcomes such as hypothyroidism, intrauterine growth retardation in the fetus, and aplasia cutis, esophagus, and choanal atresia, especially in the use of methimazole (7). Radioiodine treatment is contraindicated during pregnancy, and the second trimester is the most appropriate time in cases that require surgery.

There are maternal and fetal adverse effects of hyperthyroidism on pregnancy. Maternal complications include pre-term labor, miscarriage, preeclampsia, and heart failure (8). Fetal complications include low birth weight, goiter, and thyroid dysfunction. To minimize these negative consequences, it is important to treat the patients appropriately and to follow the mother and fetus closely.

In this study, we aimed to evaluate the effect of thyrotoxicosis on newborn weight in pregnant women with GTT or Graves' disease who were referred for thyrotoxicosis in the first trimester.

MATERIAL AND METHOD

The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 25.02.2020, Decision No: 17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

The current study is of retrospective design. Ninety-four pregnant women in the first trimester who applied between January 2016 and December 2019 with subclinical or overt hyperthyroidism and 30 healthy pregnant women in the same trimester were included in the study. All of the pregnant women included in the study had singleton pregnancies. Clinical and laboratory findings were used in the differential diagnosis of the etiology of thyrotoxicosis. Thyroid ultrasonography and Doppler were performed in all patients. TRAb was measured in all patients. As a result of these evaluations, 81 of the patients were included in the GTT group, and 13 patients had Graves’ disease. Four of the pregnant women in the GTT group were excluded from the study because of abortion. Infant birth weights were documented from the birth records of the patients. The birth weights of the babies of the GTT, Graves’ disease groups, and the healthy pregnant group were compared.

Statistical analyses of the data were performed with the IBM SPSS Statistics 21.0 package program. Nonparametric tests were used. p<0.05 was considered statistically significant.

RESULTS

77 of 81 pregnant women with GTT reached delivery. The mean age of the pregnant women with GTT was 28.7±5.2, and the mean birth weight of their babies was 3165±480 grams. The mean age of the pregnant women diagnosed with Graves’ disease was 26.2±5.3, and the mean birth weight of their babies was 3420±260 grams. The mean age of healthy pregnant women was 26.6±4.7, and the mean birth weight of their babies was 3270±350 grams (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Gestational thyrotoxicosis (n: 77)</th>
<th>Graves’ disease (n: 13)</th>
<th>Healthy controls (n: 30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers’ age (years)</td>
<td>28.7±5.2</td>
<td>26.2±5.3</td>
<td>26.6±4.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>3165±480</td>
<td>3420±260</td>
<td>3270±350</td>
<td>&gt;0.05</td>
</tr>
</tbody>
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No statistical difference was found in terms of birth weights of the babies in the comparison between the GTT group and the control, the Graves disease group and the control, and both hyperthyroidism groups (p>0.05).

While TRAb was positive in pregnant women diagnosed with Graves’ disease, this situation was not found in the GTT group. Among the patients who were followed up for Graves’ disease, 8 patients received ATT, and ATT was discontinued because 5 of these patients became euthyroid in the first trimester and 3 of them became euthyroid in the second trimester. Only 5 of the patients with GTT needed ATT. In these patients, euthyroidism was achieved in a short time and the treatment was discontinued. No thyroid dysfunction or any other drug-related adverse outcome was found in the babies of the patients who received ATT.

DISCUSSION

In our study, 77 pregnant women with GTT and 13 pregnant women with Graves’ disease were compared with 30 healthy pregnant women in terms of birth weight and no difference was found between the groups.

The incidence of GTT, which is the most common cause of thyrotoxicosis in the first trimester of pregnancy, is around 2-3% (9). It usually occurs as subclinical hyperthyroidism and thyroid function tests return to normal in the second trimester with the course of pregnancy. However, in some cases, it may present as mild overt hyperthyroidism due to excessive hCG stimulation. In these patients, the duration of thyrotoxicosis
may be prolonged and they may need ATT. In a study of patients with hyperemesis gravidarum with greater hCG stimulation, it was shown that GTT-related TSH suppression improved in approximately 19 weeks (10).

One of the most comprehensive studies investigating the effects of GTT on pregnancy outcomes was conducted with more than 25,000 pregnant women, and no difference was found in 433 pregnant women with subclinical hyperthyroidism in terms of pregnancy complications, and mortality and morbidity compared to healthy pregnant women (11). In another study conducted more recently, with 7976 pregnant women, 208 of whom had GTT and the others had normal thyroid functions, no relationship was found between GTT and low birth weight (12). In another recent study conducted in our country, no difference was found in terms of birth weight between 45 pregnant women with GTT and 45 healthy pregnant women (13). On the other hand, in the study of Medici et al. (14) evaluating the relationship between fT4 levels and birth weight in 4464 euthyroid healthy pregnant women, it was found that fT4 levels, which were within the reference range but close to the upper limit, were associated with low birth weight. In our study, in parallel with the literature, no difference was found between pregnant women with GTT and healthy pregnant women in terms of birth weight. However, the potential effect of even variation within normal reference ranges on birth weight, which was demonstrated in the study of Medici et al. may be a warning that GTT, which is not thought to cause adverse pregnancy outcomes, is still a condition that requires careful follow-up.

Graves' disease, which is the second most common cause of hyperthyroidism in pregnancy, occurs at a rate of 0.1-1% (1). Hyperthyroidism due to Graves' disease usually tends to remission later in pregnancy. The decrease in TRAb levels due to immunosuppression as gestation progresses and the change in the stimulatory type activity of TRAb to the blocking type may play a role in this (15,16). However, ATT may be required in the first trimester, depending on the severity of the clinical findings of insufficient weight gain and overt hyperthyroidism. Therefore, it is important to differentiate between GTT and Graves' disease. Severe clinical manifestations up to thyroid storm may be seen in some patients and ATT may need to be maintained throughout pregnancy (17).

It is known that overt hyperthyroidism may be associated with low birth weight (18,19). In a study comparing 180 pregnant women with overt hyperthyroidism and 360 healthy pregnant women, a 1.4-fold increase was found in the risk of low birth weight in pregnant women with hyperthyroidism (20). In a study comparing 408 pregnant women with Graves' disease with an equal number of healthy pregnant women, low birth weight rates were found at 23.7% vs. 17.7%, high in patients with Graves' disease. However, unlike the previous literature data, no difference was found in terms of birth weights between Graves' disease patients who were under control and those who were not (21). In the study of Millar et al. (22), while the risk of low birth weight was 2.36 fold in the group under control with ATT, it was reported that the risk increased by 9.24 fold in uncontrolled hyperthyroidism. In our study, no difference was found in terms of birth weight between 13 pregnant women with Graves' disease and those with GTT and the healthy control group. Since the treatment of 8 patients who received ATT treatment was discontinued in a short period, and all patients reached the term euthyroid, therefore, a comparison could not be made between the groups who received and did not receive treatment. Since the number of patients in the GTT group who needed ATT was lesser and ATT was discontinued in a short period in these patients, an in-group comparison could not be made either.

Since the etiology of the cases that resulted in miscarriage in the GTT group was due to obstetric reasons, these patients were excluded from the evaluation. Due to the relatively small number of patients with Graves' disease, we think that our sample is insufficient to evaluate the risk of low birth weight in this patient group. However, we obtained similar results to the literature in the GTT group.

CONCLUSION

Since GTT is a condition that generally tends to improve in the normal course of pregnancy, it is mostly unrelated to the risk of low birth weight. However, although it tends to alleviate in the second and third trimesters, since there may be a risk of low birth weight in Graves' disease, it can be said that the differential diagnosis of Graves' disease should be made in pregnant women who present with subclinical or overt hyperthyroidism in the first trimester. Adverse pregnancy outcomes can be reduced with appropriate treatment within indications and close perinatal follow-up.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 25.02.2020, Decision No: 17).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES