Role of Maternal Thyroid-Stimulating Immunoglobulin in Graves' Disease for Predicting Perinatal Thyroid Dysfunction

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Abstract

Objective   To assess maternal thyroid-stimulating immunoglobulin (TSI) as a predictor of neonatal thyroid hyperthyroidism in pregnancies complicated by Graves' disease.

Methods   This is a 10-year retrospective study of patients with a history of Graves' disease and elevated TSI activity level defined as 1.3 times the normal. All subjects underwent cordocentesis for ultrasound findings of suspected fetal thyrotoxicosis (fetal tachycardia, oligohydramnios, hydrops, and thyromegaly). Neonatal diagnosis was made based on neonatal thyroid function testing or symptoms.

Results   Fourteen patients were included in the study, seven with active Graves' disease requiring antithyroid drug ("ATD group") and seven with iatrogenic hypothyroidism on levothyroxine ("levothyroxine group"). Four cases (57%) of neonatal thyrotoxicosis were diagnosed in the levothyroxine group compared with two cases (28%) in the ATD group. The lowest maternal TSI level at which a neonate did not develop hyperthyroidism was 2.6 for the levothyroxine group and 2.5 for the ATD group. The odds ratio of a neonate from the levothyroxine group developing hyperthyroidism compared with one from the ATD group is 3.3 (95% confidence interval: 0.4–30.7).

Keywords
► TSI
► Graves' disease
► thyroid dysfunction

Conclusion   For patients with Graves' disease, those with iatrogenic hypothyroidism and TSI > 2.5 times the basal level are at the highest risk for neonatal thyrotoxicosis.

Thyroid disorders are the most common endocrinopathies in women of reproductive age, with overall prevalence for hyperthyroidism in the United States at 1.2%.[1] During pregnancy, hyperthyroidism is less common at 0.1 to 0.4%, but Graves' disease accounts for 85% of these cases.[2,3]

Graves' disease poses significant risks to the pregnancy and the fetus. Patients with hyperthyroidism in pregnancy are at increased risk of spontaneous abortion, fetal growth restriction, and stillbirth.[4,5] Neonates born to these mothers exhibit hyperthyroidism in 2 to 5% of cases, which can present immediate and long-term challenges including cardiac insufficiency, liver dysfunction, and psychomotor disabilities.[6–9]

Assessment of fetal thyroid dysfunction is difficult in utero, as it can involve invasive procedures such as cordocentesis in addition to serial ultrasounds. Studies have investigated maternal thyroid autoimmune antibodies as an alternative method in predicting fetal thyroid function. The antibodies have been shown to be persistently elevated despite successful treatment of Graves' disease[10] and can cross the placenta to influence fetal thyroid activity.[11]

Much attention has focused on the role of thyroid-stimulating hormone (TSH) receptor antibodies (TRAb). The American Thyroid Association recommends close monitoring of fetal status for patients who have a maternal TRAb level three times the upper limit of normal.[12] However, TRAb refers to the general class of immunoglobulin binding to the TSH receptor, which includes thyroid-stimulating immunoglobulin (TSI) and blocking antibodies.[13] Graves' disease is directly associated with the function of TSI, and thus, this marker may be a more sensitive predicator for neonatal hyperthyroidism.

There is currently no specific reference level defining the elevation of maternal TSI at which the fetus is at increased risk for thyroid dysfunction. The aim of this study is to determine the threshold maternal TSI level above which additional fetal monitoring is needed to detect perinatal hyperthyroidism. We also assessed the value of cordocentesis in patients with elevated TSI.

Methods

We conducted a retrospective study over a 10-year period at the Fetal Diagnosis and Treatment Center at the University of Iowa that focused on patients who had a history of Graves' disease and an elevated TSI level at the initial establishment of prenatal care. Those who underwent cordocentesis for reasons of abnormal ultrasound findings were included in the study. All mothers were managed and kept at the euthyroid state.

In cases clinically suspected of fetal thyroid dysfunction, the women were counseled regarding the option of cordocentesis for confirmation of the fetal diagnosis. Indications included sustained fetal tachycardia, intrauterine growth restriction (IUGR) (estimated fetal weight <10th percentile), oligohydramnios (amniotic fluid index < 5 cm), fetal hydrops, or gross fetal thyromegaly. In utero diagnosis of thyroid dysfunction were based on reference ranges of free T4 (FT4) and TSH established by Thorpe-Beeston et al's study.[14]

After delivery, cord blood was collected for thyroid function tests (TSH, FT4, and TSI). Subsequent neonatal evaluation and management depended on the clinical assessment of the attending neonatologists. Neonatal hypothyroidism was defined as FT4 below the 5th percentile and TSH above the 95th percentile. Neonatal hyperthyroidism (or thyrotoxicosis) was diagnosed by FT4 above the 95th percentile and TSH below the 5th percentile. Treatment of neonatal thyroid dysfunction was at the discretion of the neonatologists based on neonatal thyroid assessment.

TSI was quantified in sera using a commercial semiquantitative bioassay (TSI Assay, ARUP Laboratories, Salt Lake City, UT). The value for TSI is represented as a multiple above the basal activity level of the immunoglobulin. All other maternal and neonatal thyroid markers (FT4, TSH) were determined using an in-house automated immunoassay analyzer.

Data was analyzed with Minitab Statistical Software Version 18 (State College, PA).

Results

We identified 14 women with a history of Graves' disease who underwent indicated cordocentesis (►Table 1). Seven of the 14 participants had active disease during pregnancy requiring treatment with an antithyroid drug (ATD) (referred to as "ATD group"); the other seven who became hypothyroid following prior radioiodine therapy were on levothyroxine during pregnancy ("levothyroxine group").

All participants had an elevated TSI level above the threshold of 1.3, which represents 133% above the basal activity level. The 1.3 is the current maternal cutoff above which a patient is diagnosed with Graves' disease.[15] The average TSI for the hyperthyroid group was elevated at 12.0 and for the hypothyroid group at 16.8. Cordocentesis was performed in the second trimester when indicated by abnormal ultrasound findings. Fetal tachycardia was the most common abnormality across both groups with 7 of 14 cases. Interestingly, oligohydramnios and IUGR were only seen in the maternal levothyroxine group, while two cases of thyromegaly and one of pericardial effusion were observed in the ATD group.

The diagnosis of fetal thyroid dysfunction based on cordocentesis matched the neonatal outcome for 11 of 14 cases (79%). Six neonates were diagnosed with hyperthyroidism (6 of 14, 43%), 4 from the levothyroxine group and 2 from the ATD group. All six neonates required treatment with ATD.

Four neonates (cases 1, 3–5) in the maternal levothyroxine group received in utero treatment because of fetal hyperthyroidism diagnosed through cordocentesis. The mothers were prescribed propylthiouracil (PTU) in the antepartum period at the discretion of the physician. Three of the four (75%) neonates continued to be hyperthyroid after delivery.

Six preterm deliveries (6 of 14, 43%) occurred from $30^{0/7}$ to $36^{6/7}$ gestational weeks. Four were from the levothyroxine group, while two were from the ATD group. All other deliveries were at term. There was no neonatal demise in the study.

The lowest maternal TSI level at which the infant did not develop hyperthyroidism was 2.6 for the levothyroxine group and 2.5 for the ATD group.

Discussion

Neonatal hyperthyroidism has mostly been described in the context of maternal Graves' disease. In theory, the disease process is initiated by the transfer of maternal TSI to the fetal circulation, leading to increased fetal thyroid activity. TRAb is the hallmark of Graves' disease and while titers may fluctuate depending of treatment, studies have shown that ~10% of patients remain TRAb positive after medical or surgical treatment.[10,16]

Encompassed in the TRAb class of antibodies are two types of immunoglobulins, TSI and thyroid blocking antibodies. TSI directly activates the TSH receptor and leads to increase in thyroid hormone secretion.[17,18] Thus, transplacental passage of these antibodies can lead to in utero

Table 1 Maternal characteristics and subsequent neonatal outcomes of mothers with Graves' disease

Group	ID	Thyroid medication	Maternal TSI	Ultrasound findings	Diagnosis based on cordocentesis	Neonatal TSI	Neonatal diagnosis	Neonatal treatment
Levothyroxine	1[a]	Levothyroxine	13	Tachycardia	Hyperthyroidism	8.4	Hyperthyroidism	Methimazole
	2	Levothyroxine	2.6	Oligohydramnios	Euthyroid		Euthyroid	–
	3[a]	Levothyroxine	8.5	Oligohydramnios	Hyperthyroidism	17	Euthyroid	–
	4[a]	Levothyroxine	13	Tachycardia	Hyperthyroidism	12	Hyperthyroidism	Methimazole
	5[a]	Levothyroxine	3.3	Oligohydramnios, tachycardia	Hyperthyroidism	6.3	Hyperthyroidism	Methimazole
	6	Levothyroxine	5.4	IUGR, oligohydramnios	Euthyroid		Euthyroid	–
	7	Levothyroxine	30	IUGR, oligohydramnios, tachycardia	Hyperthyroidism	20	Hyperthyroidism	Methimazole
ATD	8	Propylthiouracil	5.7	Tachycardia	Hyperthyroidism		Hyperthyroidism	Methimazole
	9	Propylthiouracil	5.8	Thyromegaly	Hypothyroidism		Euthyroid	–
	10	Propylthiouracil	2.5	Small AC	Euthyroid		Euthyroid	–
	11	Propylthiouracil	11	Tachycardia	Euthyroid		Euthyroid	–
	12	Propylthiouracil	70	Thyromegaly, pericardial effusion, tachycardia	Hyperthyroidism	10	Hyperthyroidism	Methimazole
	13	Propylthiouracil	16	Small AC	Euthyroid		Euthyroid	–
	14	Propylthiouracil	6.7	Tachycardia	Hyperthyroidism	7.6	Euthyroid	–

Abbreviations: AC, abdominal circumference; ATD, antithyroid drug; IUGR, intrauterine growth restriction; TSI, thyroid-stimulating immunoglobulin.
[a]Received in utero propylthiouracil treatment.

thyrotoxicosis that continue into the neonatal period until the disappearance of the transmitted antibodies, usually within the first 3 months of life.[19]

The bulk of literature on correlation between maternal thyroid antibodies and the development of neonatal thyrotoxicosis have focused on TRAb.[20–22] There are few published reports on TSI and its effect on the perinatal outcome.[11,19,23] To our knowledge, our study of 14 patients who underwent cordocentesis is the largest study that systematically assessed the relationship of maternal TSI and its impact on neonatal thyroid dysfunction.

We found that the threshold of 2.6 was the maternal TSI level below which neonatal thyroid dysfunction was not diagnosed in the levothyroxine group and 2.5 for the ATD group. The two thresholds are comparable, suggesting that a universal TSI threshold level can be set at 2.5 regardless of maternal history. The value 2.5 represents the TSI activity level that is 250% above the basal TSI activity.

However, our study also demonstrates that maternal thyroid history should not be overlooked. More cases of neonatal thyrotoxicosis were observed in the maternal levothyroxine group than the ATD group. The odds ratio of a neonate diagnosed with hyperthyroidism from a mother on levothyroxine compared with a neonate from a mother on ATD was 3.3 (95% confidence interval: 0.4–30.7). This may be partially explained by the transfer of ATD across the placenta.[24,25] The fetuses in the ATD group of our study would have incidentally been receiving treatment in utero. Maternal transfer of ATD can also delay the diagnosis of neonatal thyrotoxicosis as the drug takes up to 7 to 10 days to be eliminated from the neonatal system.[26] However, in our study population, the diagnose of euthyroidism remained unchanged in the neonatal period. Our findings suggest that maternal treatment history for Graves' disease should be taken into account when monitoring patients with elevated TSI, particularly if the patient received radio-iodine treatment in the past.

Four fetuses in the study were intentionally treated in utero, all in the maternal levothyroxine group. The mothers were prescribed PTU based on diagnosis of fetal hyperthyroidism through cordocentesis and the doses were titrated based on repeated cordocentesis values. However, three of the four treated fetuses persisted to have thyrotoxicosis in the neonatal period requiring treatment. The mixed response in our study to in utero fetal hyperthyroid treatment is consistent with the lack of evidence-based strategy to dose PTU. In previously published cases of in utero treatment, variable neonatal outcomes were observed with a majority of infants still exhibiting symptoms of thyrotoxicosis.[27,28]

The limitations of this study include the possible lack of generality from being conducted at a single tertiary institution. Management of maternal and fetal status was further individualized at the discretion of the physician. However, our findings are based on objective data acquired through detailed longitudinal follow-up. Despite the retrospective nature, our study correlates neonatal outcome with maternal data and in utero fetal testing, which can be difficult to replicate in a prospective manner.

Conclusion

While cordocentesis appears to be accurate in prenatal diagnosis of fetal hyperthyroidism, it does not help with the management of the disease. As there lacks an adequate in utero treatment for fetal thyroid dysfunction, maternal TSI and maternal history may enable physicians to identify high-risk populations at preconception to optimize their care and outcome. We found that mothers with Graves' disease and a TSI level of 2.5 or above have an increased risk of giving birth to neonates with thyrotoxicosis. This risk can be further stratified by the type of maternal treatment for Graves' disease, with the highest clinical suspicion for mothers with iatrogenic hypothyroidism.

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