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Neonatal Graves Disease Caused by Transplacental Antibodies

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Objectives

After completing this article, readers should be able to:

1. Describe the normal physiology of the development of the thyroid gland in the fetus and the passage of hormones and antibodies during pregnancy.
2. State the incidence of thyroid autoimmune disease in the fetus and newborn of a mother who has thyroid autoimmune disease.
3. Recognize the symptoms suspicious for fetal hyperthyroidism.
4. Recognize and diagnose neonatal hyperthyroidism
5. Delineate an approach in the management of the newborn born to a mother who has autoimmune thyroid disease.

Abstract

Autoimmune thyroid disease is common in pregnancy. Graves disease is present in about 0.2% of pregnancies, and clinical hyperthyroidism occurs in approximately 1% of neonates born to women who have Graves disease. Antibodies to the thyroid-stimulating hormone receptor (TSH-R) (stimulating or blocking) freely cross the placenta and can act in the fetal thyroid gland during the second half of pregnancy. A few cases of fetal hyperthyroidism or hypothyroidism related to maternal TSH-R antibodies (TRAbs) have been reported. Neonatal hyperthyroidism or thyrotoxicosis is usually apparent by 10 days after birth. Such states should be considered emergencies and treated promptly to prevent damage in the newborn.

Introduction

Autoimmune thyroid disease is common in pregnancy and is considered a disorder of immunoregulation. Graves and Hashimoto disease, both of which can affect the fetus and newborn, share a number of characteristics but also exhibit important differences.

The prevalence of overt thyroid disease in pregnant women is 1%; there is also a 2% to 3% prevalence of subclinical hypothyroidism and 10% to 15% prevalence of antibody positivity. (1) Graves disease is present in about 0.1% to 0.4% of pregnancies, and clinical neonatal hyperthyroidism occurs in only 1% of neonates born to mothers who have Graves disease. (2)(3) There is considerable heterogeneity of the response to maternal thyroid antibodies; even among identical twins, the uptake and metabolism of thyroid-stimulating antibodies may be dissimilar. (4)

The first case of fetal hyperthyroidism probably due to maternal antibodies was described by White in 1912; he had suspected the condition to be present before birth in the fetus of a woman who had thyrotoxicosis. The infant died at 38 hours of age of a subdural hemorrhage. (5)

It is well known that maternal thyroid antibodies, especially antibodies to the TSH-R, freely cross the placenta and can act in the fetal thyroid gland during the second half of

Abbreviations

ATD:	antithyroid drug
FT3:	free triiodothyronine
FT4:	free thyroxine
T4:	thyroxine
TRAb:	thyroid-stimulating hormone receptor antibody
TRH:	thyrotropin-releasing hormone
TSAb:	thyroid-stimulating hormone-stimulating antibody
TSBAb:	thyroid stimulating hormone-blocking antibody
TSH:	thyroid-stimulating hormone
TSH-R:	thyroid-stimulating hormone receptor

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pregnancy. (6) Thyroid hormone is essential for the growth and maturation of many target tissues, including the brain and skeleton. As a result, abnormalities of thyroid gland function in the fetus and newborn may have not only metabolic consequences but also affect the growth and maturation of thyroid hormone-dependent tissues. Early diagnosis and treatment of fetal hyperthyroidism or hypothyroidism are crucial to prevent preterm delivery, death in utero, or permanent impairment. This is the reason why the Endocrine Society, in association with other international societies, recently published guidelines for the management of thyroid dysfunction during pregnancy and after birth. (1)

Development of the Fetal Gland and Passage of Thyroid Hormones

The thyroid gland is derived from the fusion of a medial outpouching from the floor of the primitive pharynx, the precursor of the thyroxine (T4)-producing follicular cells, and bilateral evagination of the fourth pharyngeal pouch, which give rise to the parafollicular (calcitonin)-secreting cells. (7) Growth and descent of the thyroid gland into the neck result from the coordinated action of a number of transcription factors. (8)

Embryogenesis is largely completed by 10 to 12 weeks' gestation, and the fetal thyroid gland starts secreting thyroid hormones around week 12. In addition, fetal TSH-Rs become responsive to TSH and TRAbs around week 20. (9)(10)(11)

From gestational week 12, fetal thyroid hormones continue to increase gradually, concomitant with an increase in serum T4-binding globulin. There is also a progressive increase of free T4 (FT4) between 18 and 36 weeks, indicating maturation of the hypothalamic-pituitary-thyroid axis. Maternal T4 crosses the placenta in small amounts during the first half of pregnancy, when fetal thyroid hormone concentrations are low. The placenta is freely permeable to thyrotropin-releasing hormone (TRH), but transplacental passage of TSH or thyroglobulin is absent. Instead, maternal TRAbs readily cross the placenta. Therefore, the fetal thyroid gland may be affected by antithyroid drugs (ATDs) and radioactive iodine from week 12 and by antibodies during the third trimester of pregnancy.

Transplacental Passage of Maternal Thyroid Antibodies

As in other autoimmune diseases, specific maternal immunoglobulin (immunoglobulin G) crosses the placenta by an active transfer, largely during the last trimester of pregnancy. Recognized antithyroid antibodies include TRAbs. The first observation of what eventually turned out to be stimulating antibodies against TSH was made in 1956 by Adams and Purves. (12) This substance originally was believed to be an abnormal TSH.

These antibodies can compete with TSH for binding to the TSH-R, while stimulating (TSAb) or blocking (TSBAb) TSH. The transplacental transfer of TRAb can be seen at 21 weeks' gestation. The amount of TRAb changes during the course of pregnancy. At delivery and in the following months, the maternal and neonatal TRAbs are mostly TSAbs. (13)(14) Although other antibodies, such as antithyroglobulin and antithyroid peroxidase, can cross the placenta, they do not appear to produce major effects in the newborn, despite an association with a significant increment in miscarriages. (1)

TRAbs are given different names and are assayed by several methods. They are measured using commercial kits that record the percentage of inhibition of TSH binding to a membrane preparation of TSH-Rs. The assay does not measure the ability of the antibody to stimulate the receptor. (1) Thyroid-stimulating immunoglobulin assays are also available.

Maternal Graves Disease and Effects in the Fetus and Newborn

Graves disease is present in 0.2% (0.1% to 0.4%) of pregnancies. Maternal antibodies to the TSH-R that crossed the placenta stimulate the TSH-Rs located on the epithelial cells of the fetal thyroid gland.

The first report that specifically suggested that TSAbs were implicated in neonatal thyrotoxicosis appeared in 1960. (15) The authors reported a woman who twice had given birth to an infant who died within a few days from severe hyperthyroidism. The mother's serum revealed high titers of antibodies. Since that date, a few cases of fetal hyperthyroidism related to maternal TRAbs have been reported. Such conditions may develop in fewer than 1% of pregnancies.

In the absence of maternal treatment with ATDs, hyperthyroidism develops in the fetus during the second half of pregnancy. (16) Hyperthyroidism can develop even in the presence of ATD therapy if the titer of TRAbs is high. Early diagnosis may prevent preterm delivery and death in utero. The clinical picture includes fetal tachycardia, intrauterine growth restriction, fetal goiter, accelerated bone maturation, fetal cardiac failure, or fetal hydrops. Ultrasonography that reveals fetal goiter is a valuable finding, but goiter can be difficult to detect and measure. (17)(18)(19) If the diagnosis cannot be inferred adequately on clinical grounds, cord blood sampling to measure TSH, FT4, and TRAb may make the

definitive diagnosis and help in the prompt institution of treatment. (1)(14) Neonatal hyperthyroidism has a reported incidence of 1% in neonates born to mothers who have Graves disease. Maternal TRAbs continue to stimulate the neonatal thyroid after birth, resulting in abnormal thyroid function in early infancy. The infant eventually develops clinical symptoms within the first postnatal month. Late-onset neonatal hyperthyroidism, occurring at about 45 days of age and persisting for more than 6 months, also has been reported, (18)(20) but usually is apparent by 10 days of age. (21)

The clinical manifestations of neonatal hyperthyroidism may be mild or severe (thyrotoxicosis) and include: (1)(18)(21)

- Intrauterine growth restriction
- Goiter
- Central nervous signs: irritability, jitteriness, and restlessness
- Ophthalmologic signs: periorbital edema, lid retraction, and exophthalmos
- Cardiovascular signs: tachycardia, arrhythmias, cardiac failure, and pulmonary hypertension
- Signs of hypermetabolism: voracious appetite, weight loss, diarrhea, sweating, and flushing
- Advanced bone age, craniosynostosis, and microcephaly
- Other: persistent acrocyanosis, hepatosplenomegaly, lymphadenopathy, thymic enlargement, bruising, and petechiae

Neonatal thyrotoxicosis usually remits after 8 to 20 weeks. Virtually all infants are euthyroid by 48 weeks' postnatal age. Rarely, thyrotoxicosis persists. (22)(23) Babies at high risk for congenital hyperthyroidism due to maternal Graves disease, especially those who have had evidence of thyrotoxicosis in utero, those whose mothers are receiving antithyroid treatment at the time of delivery, and those whose mothers have high titers of TRAb, may require close observation in the hospital for the first few days after delivery and should be monitored by measuring free triiodothyronine (FT3), FT4, and TSH and undergoing serial physical examinations. FT4 and TSH should be measured between postnatal days 10 and 14. (18)(21)

Symptomatic neonatal hyperthyroidism should be considered an emergency and treated quickly. Medical treatment includes the antithyroid thionamides propylthiouracil and carbimazole (methimazole), which block thyroid hormone synthesis and inhibit the peripheral conversion from T4 to more active hormone T3. (24) Beta blockers, which are effective in controlling symptoms and inhibit the peripheral conversion from T4 to T3, and iodine solution, which suppresses thyroid hormone synthesis, are also useful. (21)

Current recommendations state that breastfeeding should continue, and both ATDs are considered safe. Both appear in human milk (methimazole more than propylthiouracil) but in low concentrations. Clinical studies of breastfed infants have shown that they have normal thyroid function. (24)

Conclusions

Symptomatic neonatal hyperthyroidism should be considered a medical emergency. Prompt and adequate institution of treatment may prevent severe damage in the newborn. Graves disease during pregnancy needs to be monitored closely to avoid complications due to the free passage of antibodies through the placenta and the development of clinical manifestations.

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NeoReviews Quiz

9. The thyroid gland is derived as a medial outpouching from the floor of the primitive pharynx. Growth and descent of the thyroid gland into the neck during development result from a coordinated action of a number of transcription factors. The fetal thyroid gland starts secreting thyroid hormone around gestational week:

   A. 8.
   B. 12.
   C. 16.
   D. 20.
   E. 24.

10. A 34-year-old primigravid woman is carrying a fetus at an estimated gestational age of 28 weeks. Her history is significant for hypothyroidism due to autoimmune thyroiditis diagnosed 4 years earlier for which she is receiving thyroid hormone treatment. She inquires whether the thyroid hormone can cross the placenta and affect the thyroid function of her fetus. Of the following, the hormone *most* readily transferred across the placenta is:

    A. Tetraiodothyronine.
    B. Thyroglobulin.
    C. Thyroid-stimulating hormone.
    D. Thyrotropin-releasing hormone.
    E. Triiodothyronine.

11. In maternal Graves disease, specific thyroid antibodies can cross the placenta and act on the fetal thyroid gland during the second half of pregnancy. Of the following, the maternal antibody *most* likely to produce major effects on the thyroid gland of the newborn is the:

    A. Antinuclear antibody.
    B. Antithyroglobulin antibody.
    C. Antithyroid peroxidase antibody.
    D. Colloid antigen antibody.
    E. Thyroid-stimulating hormone-receptor antibody.

12. Maternal Graves disease occurs in about 0.1% to 0.4% of pregnancies and can cause neonatal hyperthyroidism with clinical manifestations that typically become apparent by 10 days after birth. Of the following, the incidence of hyperthyroidism among neonates born to mothers who have Graves disease is *closest* to:

    A. 1%.
    B. 10%.
    C. 30%.
    D. 50%.
    E. 70%.

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