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OBJECTIVES

After completing this article, readers should be able to:

1. **Describe the etiology of transient and persistent neonatal hyperthyroidism.**
2. **Delineate the diagnostic tests for thyroid-stimulating hormone receptor antibodies.**
3. **Develop a treatment plan for fetal and neonatal hyperthyroidism and a management plan for subsequent pregnancies.**
4. **Provide guidelines for breastfeeding when the mother is receiving antithyroid medications.**
5. **Describe the long-term risks of neonatal hyperthyroidism.**

History

The first clinical description of neonatal hyperthyroidism was published in 1912, and the discovery of the transplacental passage of thyroid-stimulating immunoglobulins (TSI) provided an understanding for the etiology of this condition in 1964. There were, however, a few cases of persistent neonatal hyperthyroidism, initially described in 1976, that were inconsistent with the transient clinical course expected with a maternally acquired antibody. The etiology of persistent neonatal hyperthyroidism was clarified by the discovery of an activating germ-line mutation in the thyroid-stimulating hormone (TSH) receptor in 1995.

Maternal Autoimmune Thyroid Disease

When a mother has autoimmune thyroid disease, fetal and neonatal hyperthyroidism result from transplacental passage of TSI. The mother usually has a history of hyperthyroidism, but neonatal hyperthyroidism also has been reported in mothers who have hypothyroidism due to Hashimoto thyroiditis. The clinical status of the mother does not determine the infant's risk for hyperthyroidism. The mother may have been treated with ^{131}I or a subtotal thyroidectomy in the past and may be euthyroid or she may be receiving thyroid replacement therapy at the time of her pregnancy, but she still can be producing high titers of TSI. In a review of neonatal hyperthyroidism, mothers were clinically hyperthyroid during pregnancy in only 18 of 38 cases (47%). The prevalence of clinical hyperthyroidism in pregnancy has been reported to be 0.1% to 0.4% and is the most common endocrine disorder during pregnancy after diabetes. Clinical fetal and neonatal hyperthyroidism has been reported to occur in 1% to 5% of pregnancies complicated by Graves disease. It is common for fetal and neonatal hyperthyroidism to recur in subsequent pregnancies.

Why is there such a low incidence of neonatal hyperthyroidism with all the mothers who have autoimmune hyperthyroidism producing TSI? Several pregnancy-related immunologic events work concomitantly to lower the fetal/neonatal risk for hyperthyroidism. The TSH receptor is present in the fetus at 12 weeks of gestation, but before 15 weeks of gestation, fetal immunoglobulins are only 5% to 8% of maternal levels, so little TSI crosses the placenta. By 30 weeks of gestation, when fetal immunoglobulin levels are equal to maternal levels, there is a decrease in TSI concentrations due to immune suppression that occurs during pregnancy. When measured serially in 15 mothers who had hyperthyroidism, TSI levels decreased from 280% in the first trimester to 130% in the third trimester. In general, there is a risk of fetal/neonatal hyperthyroidism only in pregnancies in which the mother is producing high titers of TSI.

TSI

The nomenclature of commercial assays used to measure antibodies that bind to the TSH receptor is somewhat confusing (Table). Some of the assays measure binding to the receptor and others measure how the antibody binding is affecting receptor function. TSH receptor antibodies may stimulate or inhibit the receptor, and patients may have combinations of different types of antibodies. TSH-binding inhibitory immunoglobulins (TBII) are measured by a competitive radioreceptor assay using thyroid membrane extracts and labeled TSH, and the result is expressed as a percent inhibition of TSH binding. This assay measures whether the antibody has bound to the TSH receptor, but does not measure whether the antibody stimulates or inhibits the receptor. TSI now are measured commonly using TSH receptor-transfected Chinese hamster ovary (CHO) cells, and stimulation is measured by the generation of adenosine 3′,5′-cyclic monophosphate (cAMP). Results are expressed as percent stimulation above basal. TSH-blocking antibodies (TBA) are determined in the same assay system using TSH-transfected CHO cells. TSH is added in the presence or absence of the

ABBREVIATIONS

cAMP:	adenosine 3′,5′-cyclic monophosphate
CHO:	Chinese hamster ovary
IUGR:	intrauterine growth retardation
MMI:	methimazole
PTU:	propylthiouracil
TSH:	thyroid-stimulating hormone
TSI:	thyroid-stimulating immunoglobulins
TBII:	TSH-binding inhibitory immunoglobulins
TBA:	TSH-blocking antibodies
T4:	thyroxine
T3:	triiodothyronine

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TABLE. Commercial Thyroid Receptor Antibody Measurements

	METHOD	NORMAL	% ABNORMAL IN HYPERTHYROIDISM
TSH-binding Inhibitory Immunoglobulin (TBII)	Radioreceptor assay	<10% inhibition	70% to 96%
Thyroid-stimulating Immunoglobulin (TSI)	In vitro bioassay	<130% to 150% of basal	80% to 96%
TSH-blocking Antibody (TBA)	In vitro bioassay	<10% inhibition	17%

patient's serum, and blocking activity is expressed as percentage inhibition of cAMP production by the patient's serum. In a small number of pregnancies, the effect of TBA initially may dominate and delay the clinical onset of neonatal hyperthyroidism, making infants initially appear to be euthyroid or hypothyroid.

Fetal hyperthyroidism occurs with TSI levels in excess of 300% of control values or a level of TBII in excess of 30%. The half-life for anti-TSH receptor antibodies is 12 to 13 days. Clinical symptoms generally resolve in 2 to 4 months as maternal antibody titers diminish in the neonate.

To characterize better the relationship between multiple specificities of the antibodies being generated in autoimmune thyroid disease and their effects on TSH receptor function, lymphocytes from a woman who had clinical hypothyroidism and gave birth to three children in whom the onset of neonatal hyperthyroidism was delayed were studied. Lymphocytes were hybridized and cloned, and the monoclonal antibodies were characterized by their epitope binding and subsequent effect on TSH receptor function. Twelve clones had stimulating activity and bound to residues 90 to 165 on the TSH receptor extracellular domain. Four clones blocked TSH receptor responses to both TSH and TSI and bound to extracellular residues 261 to 370. Three clones bound to residues 90 to 165 and blocked the effect of TSH, but not the effect of TSI on stimulating receptor activity. A fourth clone bound to residues 24 to 89 and blocked TSH stimulation but also exhibited signal transduction activity by increasing inositol phosphate levels. These epitope binding sites are schematically presented in Figure 1.

Treatment of Maternal Hyperthyroidism

Maternal hyperthyroidism can result in adverse fetal/neonatal outcome by two mechanisms: 1) uncontrolled maternal hyperthyroidism (without high TSI levels) and 2) transplacental passage of TSI. With uncontrolled maternal hyperthyroidism, the fetus is at risk for stillbirth, intrauterine growth retardation (IUGR), and prematurity. The risk of prematurity increases from 11% in treated women to 55% in untreated women, and the risk of stillbirth increases from 5% to 24%. In a study of 230 pregnancies complicated by hyperthyroidism, 15 neonates (6.5%) suffered IUGR. Fetal complications are increased significantly in mothers who remain hyperthyroid during the second half of pregnancy. Risk factors for IUGR in this study included: 1) maternal thyrotoxicosis for 30 weeks or more during pregnancy, 2) a history of Graves disease of greater than 10 years duration, 3) onset of Graves disease before age 20, and 4) TBII levels of 30% or higher prior to delivery.

Maternal hyperthyroidism generally is treated with propylthiouracil (PTU) instead of methimazole (MMI) because of a low incidence (13 cases) of aplasia cutis congenita (a localized ulcer-like lesion in the parietal area of the scalp) associated with MMI use. Fetal exposure to MMI also has been associated with choanal atresia, esophageal atresia, and tracheoesophageal fistula. However, no teratogenicity resulted from MMI therapy in several large studies. Antithyroid treatment often is needed in the first and second trimester. Results of thyroid tests may normalize spontaneously as the pregnancy progresses because of the immunologic changes occurring during pregnancy, and in 30% of hyperthyroid pregnancies, antithyroid medication can be discontinued by 32 to 36 weeks of gestation. Part of the change in results of thyroid function tests occurring during pregnancy is due to a change in the specificity of TSH receptor antibodies from stimulating to blocking antibodies. Overdosage with antithyroid medications can result in fetal goiter and hypothyroidism because MMI and PTU readily cross the placenta. When hyperthyroidism occurs during pregnancy, PTU can be started at a dose of about 150 mg every 8 hours and MMI at a dose of 10 to 20 mg twice a day. Thyroid function tests should be re-evaluated every 2 to 3 weeks, and the dose of antithyroid medication adjusted to maintain the free thyroxine (T4) level in the upper one third of the normal range.

Propranolol is not recommended during pregnancy because of potential neonatal morbidity. Propranolol crosses the placenta, limiting cardiovascular responses to anoxia and causing respiratory depression. Infants born to mothers receiving propranolol have had low Apgar scores, prolonged bradycardia, and borderline hypoglycemia. Propranolol therapy also has increased the incidence of spontaneous abortion from 5.5% to 24.4%.

Iodide therapy during pregnancy is contraindicated because of the association with neonatal goiter and hypothyroidism. ^{131}I therapy also is contraindicated during pregnancy, particularly after 12 weeks of gestation when the neonatal thyroid is capable of concentrating iodine. If

^{131}I is administered inadvertently during the first trimester, the infant may develop congenital hypothyroidism or congenital malformations.

Thyroid surgery rarely is performed during pregnancy. It is reserved for cases of drug allergy to MMI and PTU or failure to respond to antithyroid medication (noncompliance).

Fetal Hyperthyroidism

MONITORING

A maternal serum TSI and TBII level should be determined in several circumstances: 1) a history of fetal or neonatal hyperthyroidism in previous pregnancies; 2) active hyperthyroidism during the third trimester and the mother is being treated with antithyroid medications; and 3) the mother is being treated for hyperthyroidism and there is fetal tachycardia, IUGR, or a goiter on fetal ultrasonography.

If the TSI level is greater than 300% or the TBII level is greater than 30% of control values, the fetus should be monitored closely with serial ultrasonography and fetal heart rate monitoring every 2 weeks. A TSI of more than 500% basal values in the third trimester is associated with a high incidence of fetal hyperthyroidism, and maternal antithyroid drug treatment may be necessary to control fetal symptoms even if the mother is euthyroid.

TREATMENT

The fetal heart rate is normally in the range of 120 to 160 beats/min. If the fetal heart rate is greater than 160 beats/min, antithyroid medication should be administered to the mother with a goal of maintaining a fetal heart rate of about 140 beats/min. Fetal tachycardia has been detected as early as 22 weeks' gestation, and treatment has been successful in controlling fetal tachycardia and preventing IUGR and prematurity. Serial fetal ultrasonography should be obtained to assess for fetal goiter, which can be a sign of excessive antithyroid medication, and to assess for IUGR. Fetal goiters can be detected after 27 weeks' gestation and can be associated with polyhydramnios, presumably due to obstruction of the fetal esophagus by the goiter. Fetal thyroid hormone levels can be determined definitively by cordocentesis, although this procedure is associated with a 1% rate of fetal loss and may induce fetal hemorrhage (40%), cord hematoma (17%), infection (1%), and preterm delivery (5% to 6%).

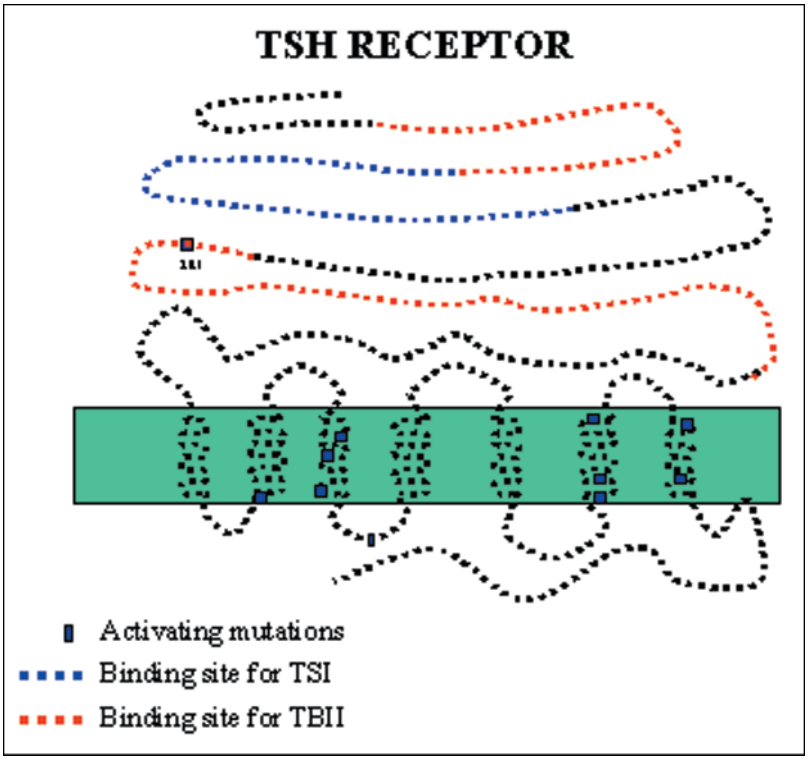

FIGURE 1. Schematic representation of the TSH receptor.

Activating Mutations in the TSH Receptor

Hyperthyroid infants born to mothers who do not have a history of autoimmune disease may have an activating mutation in their TSH receptor. These children have negative TSI and TBII antibodies, and their hyperthyroidism persists beyond the neonatal period. Treatment consists of a near-total thyroidectomy and radioiodine ablation of remaining thyroid tissue. The TSH receptor is a member of the superfamily of G-protein-coupled transmembrane receptors. It is characterized by seven transmembrane helices connected by three extracellular and three intracellular loops. Most constitutively active germ-line mutations of the TSH receptor occur in exon 10 (Fig. 1), which encodes for the entire transmembrane region of the receptor, although there is one case report of a mutation occurring in the extracellular domain of the TSH receptor causing congenital hyperthyroidism.

Germ-line mutations in the TSH receptor may present as sporadic occurrences or be inherited in an autosomal dominant pattern. There can be great variability in the age at onset of clinical manifestations, ranging from a severe presentation at birth to mild hyperthyroidism in adulthood. The incidence of these mutations causing neonatal hyperthyroidism is unknown, but in an older review of the literature, 13% (10/76) of affected infants had symptoms beyond 1 year of age. TSI were measured in only three of these cases and were negative in two. Mutations causing constitutive activation of G-protein receptors also have been described in gonadotropin-independent precocious puberty in males (luteinizing hormone receptor), hyperfunctioning thyroid adenomas, and mutations in the calcium-sensing receptor that result in autosomal dominant hypocalcemia. McCune-Albright

syndrome is due to a somatic mutation in G-protein receptors, with a mosaic distribution of these activating mutations. Clinically these children classically present with café au lait spots, polyostotic fibrous dysplasia, and gonadotropin-independent precocious puberty. An infant has been reported who had neonatal hyperthyroidism and McCune-Albright syndrome and died in cardiac failure due to hyperthyroidism at 4 months of age.

Neonatal Hyperthyroidism

LABORATORY ASSESSMENT

Newborn screening cannot be relied on to detect neonatal hyperthyroidism for three reasons. First, many programs are designed to detect primary hypothyroidism, and an abnormal result is reported only if there is an elevated TSH value. Infants who have hyperthyroidism will have a suppressed TSH level and, therefore, will not be reported. Second, fetal hyperthyroidism may transiently suppress pituitary TSH secretion. Third, at the time of screening, the newborn's thyroid status may be hypothyroid, hyperthyroid, or euthyroid, depending on transplacental passage of antithyroid medications, TSI, and TBA.

Transient neonatal hypothyroidism occurs in 0.5% to 5% of pregnancies in which the mother is taking antithyroid medications; it usually is related to the dose of maternal antithyroid medication. Antithyroid medications have a short duration of action of 24 to 48 hours. Because 95% to 99% of infants born to mothers who have Graves disease will not develop hyperthyroidism, initial assessment of these children should include a clinical examination and measurement of maternal TSI or TBII levels. An infant born to a mother in whom TSI or TBII levels are unknown should have blood drawn for thyroid function testing (T4 or free T4 and TSH) and have TSI or TBII levels drawn prior to discharge from the hospital. Determination of TSI or TBII levels on cord blood or newborn serum can be predictive of subsequent neonatal hyperthyroidism.

Skuza studied 14 infants born to mothers who had Graves disease (see Suggested Reading). Seven infants developed neonatal hyperthyroidism, all of whom had TBII concentrations greater than 0.20 in cord blood or in the first few days of life. Seven infants who had TBII levels less than 0.15 remained euthyroid. Initial measurements of TSH, T4, free T4, or triiodothyronine (T3) were not helpful in predicting subsequent hyperthyroidism. Overt thyrotoxicosis usually is present by 5 to 10 days after birth, but has been delayed until 45 days after birth in the presence TBA. Therefore, infants who have high TSI or high TBII levels should be monitored closely, undergoing thyroid function tests every 1 to 2 weeks for the first 4 to 6 weeks of life.

CLINICAL PRESENTATION

Symptoms of hyperthyroidism develop between 1 and 29 days of age, and treatment is usually required until 57 to 129 days of life. Signs and symptoms of hyperthyroidism in the newborn include:

- IUGR, prematurity
- Goiter, tracheal obstruction
- Stare, exophthalmos
- Congestive heart failure, tachypnea, tachycardia, arrhythmias
- Hypertension
- Craniosynostosis, microcephaly, frontal bossing, triangular-shaped face
- Accelerated bone age
- Hyperkinesis, diaphoresis, flushing
- Frequent vomiting or diarrhea
- Hypoglycemia
- Poor weight gain
- Hyperviscosity syndrome
- Hyperbilirubinema (direct or indirect), hepatic cholestasis
- Thrombocytopenia, petechiae
- Hepatosplenomegaly (with or without congestive heart failure)
- Lymphadenopathy
- Infections

Many of these signs and symptoms are illustrated in a 10-day-old infant who has immune-mediated neonatal hyperthyroidism (Fig. 2). She had IUGR, goiter, tachycardia, craniosynostosis, poor weight gain, and hepatosplenomegaly.

These symptoms can be confused with a congenital infection, such as toxoplasmosis, rubella, or cytomegalovirus infection. For years it has been unclear whether many of the clinical findings in neonatal hyperthyroidism resulted from autoimmunity (such as hepatosplenomegaly, exophthalmos, thrombocytopenic purpura) or the hyperthyroidism. However, it now appears that nonautoimmune neonatal hyperthyroidism due to mutations in the TSH receptor is associated with hepatosplenomegaly, thrombocytopenic purpura, jaundice, and proptosis. The exophthalmos may be explained by the presence of TSH receptors on retroorbital tissue that causes hypertrophy of these tissues.

The gender distribution of neonatal hyperthyroidism is equal. Hypertension (systolic blood pressure >100 mm Hg) has been documented between the second and third weeks of life. Congestive heart failure is thought to be due to beta-adrenergic stimulation that results in high output failure. The mortality rate has been reported at 12% to 16% and usually is associated with high output congestive failure, but diarrhea and fluid loss, tracheal obstruction by large goiters, thrombocytopenia purpura, and infections are additional hazards. Symptoms last for more than 8 weeks in over 88% of patients, but they generally resolve in 2 to 4 months. In a review of 75 infants who had hyperthyroidism, 14 (19%) had clinical courses lasting more than 6 months, and 10 (13%) had hyperthyroidism lasting for more than 1 year. Infants in whom symptoms persist for longer than 1 year may have nonimmune hyperthyroidism associated with mutations in the TSH receptor.

TREATMENT

Hyperthyroid symptoms can appear rapidly in the infant who is 12 to 48 hours of age as transplacentally acquired antithyroid medications disappear and the usual increase in T4 to T3 conversion occurs. Standard therapy generally consists of PTU, iodine drops, and propranolol. PTU should be administered 5 to 10 mg/kg per day in divided doses every 8 hours. Saturated iodine solution (10% potassium iodide, 126 mg/mL iodine) is administered

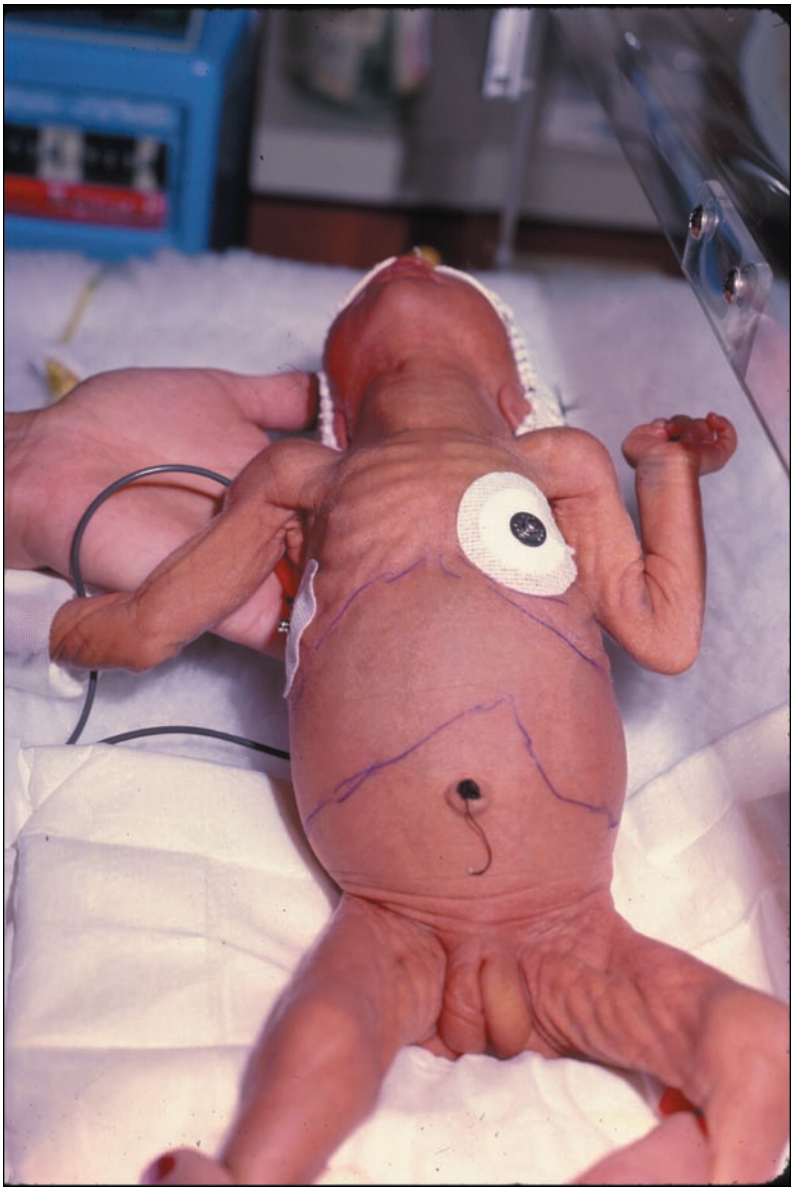

FIGURE 2. Ten-day-old infant who has immune-mediated hyperthyroidism. Note the presence of goiter and hepatosplenomegaly.

at a dose of 8 mg (one drop) every 8 to 12 hours. If there is no response in 48 hours, the dose of iodine can be doubled. Propranolol can be used to control tachycardia at a dose of 2 mg/kg per day divided bid or tid. Propranolol treatment can result in bradycardia and possibly hypoglycemia. Glucocorticoids can inhibit both thyroid hormone secretion and peripheral conversion of T4 to T3. Prednisone can be given in dose of 1 to 2 mg/kg per day.

Less traditional forms of therapy have included sodium ipodate, iopanoic acid, and exchange transfusion. Sodium ipodate inhibits extrathyroidal conversion of T4 to T3 and inhibits thyroid hormone secretion. An infant who had neonatal hyperthyroidism was treated successfully with 0.5 g every 3 days, although intermittent increases in serum T3 levels prompted a recommendation to use 0.1 to 0.2 g/day. Iopanoic acid is similar to sodium ipodate in its action and has been given at a dose of 500 mg orally every 3 days. The advantages of iopanoic acid and sodium ipodate over thionamides are a more rapid decrease in thyroid levels and no risk of treatment-induced hypothyroidism. However, there is much more experience with thionamides in the management of neonatal hyperthyroidism. Because neonatal immune hyperthyroidism is due to maternally acquired immunoglobulins, treatment with exchange transfusion has been attempted and resulted in a 50% decrease in TSI and T4 levels, although the effect was short-lived. Within 10 days the infant was clinically hyperthyroid.

Central hypothyroidism may result from pituitary suppression after fetal thyrotoxicosis. In rats that had neonatal hyperthyroidism, a permanent decrease in TSH secretory reserve persisted into adult life. In humans, the suppression of TSH secretion has been transient. It may be present at birth, after a transient period of thyrotoxicosis in neonatal Graves disease, or after nonautoimmune neonatal thyrotoxicosis. It is, therefore, important not to rely solely on TSH levels to guide treatment of neonatal hyperthyroidism; T4 (free T4) and T3 (free T3) levels also should be measured to detect central hypothyroidism.

LONG-TERM OUTCOME

In animal models of fetal hyperthyroidism, neuronal cell division is arrested prematurely, resulting in adult brains that weigh 20% to 30% less than normal and contain 30% to 40% fewer cells. This is due to increased oligodendroglial cell death by apoptosis and a substantial reduction in the amount of myelin basic protein. Hyperthyroid rats also show significant impairment in spatial learning and memory associated with morphologic alterations in the hippocampus.

Long-term follow-up of children who had fetal/neonatal hyperthyroidism has demonstrated intellectual impairment in 50% to 100% of immune-mediated cases. Learning disabilities also occur with mutations in the TSH receptor. A moderate degree of intellectual impairment often is associated with craniosynostosis. Craniosynostosis predominately involves the coronal and occasionally the sagittal suture. It may cause frontal prominence, but generally it does not impair head circumference growth or cause increased intracranial pressure. In a study of twins affected by neonatal hyperthyroidism, both twins had

microcephaly, craniosynostosis, and dilated lateral ventricles, and their intelligence quotients were 67 to 74 at 3.5 years of age. Hyperactivity, rapid mood swings, and visual-motor and perceptual-motor problems frequently are described, analogous to the changes observed in rats.

Breastfeeding by the Mother Who Has Hyperthyroidism

Because PTU is highly bound to plasma proteins, only a small amount is excreted into human milk (0.077%). MMI is not as highly bound to plasma proteins, and studies have demonstrated a milk/plasma ratio of approximately 1. A recent study followed results of thyroid function tests in 35 infants who were being breastfed while their mothers were receiving 5 to 20 mg of MMI each day. All results were normal, and there were no reported adverse events or allergic reactions. Therefore, there is no reason why mothers who have hyperthyroidism and who want to breastfeed their infants while taking antithyroid medications should not be allowed to do so. PTU is the drug of choice in these mothers because only minimal amounts appear in human milk. Breastfeeding mothers should try to take less than 200 mg/d of PTU, and they should try to take each dose after breastfeeding. Thyroid function tests should be obtained every 2 to 4 weeks in infants being breastfed by mothers receiving antithyroid medication.

Summary

Fetal and neonatal hyperthyroidism most commonly is due to transplacental passage of maternal TSI. The mother usually has a history of autoimmune disease, but she may be euthyroid, hypothyroid, or hyperthyroid during the pregnancy. Nonimmune hyperthyroidism is due to an activating mutation of the TSH receptor, may be dominantly inherited, and causes permanent hyperthyroidism. Fetal hyperthyroidism is treated by administering PTU to the mother and monitoring the fetal heart rate, growth, and goiter size. Neonatal hyperthyroidism generally is treated with PTU, iodine, and propranolol. Autoimmune neonatal hyperthyroidism generally resolves in 2 to 4 months, but nonautoimmune hyperthyroidism requires thyroid gland ablation. Both forms of neonatal hyperthyroidism may result in long-term neurologic sequelae.

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NEOREVIEWS QUIZ

Quiz also available online at www.neoreviews.org.

1. A pregnant woman who has a family history of goiter is concerned about thyroid problems during her pregnancy and in her offspring. Of the following, the *most* accurate statement about maternal and neonatal hyperthyroidism is that:
   A. Hyperthyroidism is the most common endocrine disorder during pregnancy.
   B. Levels of thyroid-stimulating immunoglobulins (TSI) increase during pregnancy.
   C. Most neonates who have hyperthyroidism are born to mothers who have clinical evidence of hyperthyroidism.
   D. Recurrence of neonatal hyperthyroidism in subsequent pregnancies is rare.
   E. The risk of neonatal hyperthyroidism is high only in the presence of high maternal titers of TSI.

2. A newborn has a large thyroid goiter that is obstructing the trachea, craniosynostosis, microcephaly, and exophthalmos. Cardiovascular examination reveals tachychardia, hypertension, and congestive heart failure. Maternal history is positive for antoimmune thyroid disease. You suspect neonatal hyperthyroidism. Of the following, the *most* appropriate treatment for this infant is:
   A. Digoxin.
   B. Exchange transfusion.
   C. Immune globulin.
   D. Propylthiouracil.
   E. Thyroid gland ablation.

The Hyperthyroid Fetus and Infant

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