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Evaluation and management of neonatal Graves' disease

Author: Stephen LaFranchi, MD
Section Editor: Mitchell E Geffner, MD
Deputy Editor: Alison G Hoppin, MD

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INTRODUCTION — Neonatal Graves' disease refers to the hyperthyroidism that is seen in a small percentage of infants born to mothers with Graves' disease. Although neonatal Graves' disease is usually self-limited, it can be severe, even life-threatening, and have deleterious effects on neural development. Maternal Graves' disease is by far the most common cause of neonatal hyperthyroidism. Active Graves' disease in a pregnant woman can lead to either hyper- or hypothyroidism in the fetus and neonate, depending on the balance of the maternal stimulatory and inhibitory antibody and antithyroid drug effect [1]. Babies destined to develop neonatal Graves' disease, however, are almost always hyperthyroid at or within one week of birth. (See "Hyperthyroidism during pregnancy: Treatment".)

INCIDENCE — Graves' hyperthyroidism occurs in approximately 0.2 percent of women, and it occurs in approximately one to five percent of infants born to these mothers [2-4]. Thus, neonatal Graves' hyperthyroidism would be expected to occur in approximately 1:25,000 neonates and affects males and females equally.

Why only 1 to 5 percent of infants of mothers with Graves' hyperthyroidism are affected is explained by the level of the maternal serum stimulatory thyrotropin (thyrotropin-stimulating hormone or TSH) receptor antibody (TSHR-Ab). The higher the maternal stimulatory TSHR-Ab concentration is during the third trimester, the greater is the likelihood of neonatal Graves' hyperthyroidism. In practice, neonatal hyperthyroidism is most likely when the TSHR-Ab activity of maternal serum is above 500 percent of the values in serum of normal subjects [5-7]. This was illustrated in a study of 29 pregnant women with a history of Graves' disease that confirmed the relationship of high TSHR-Ab and neonatal thyrotoxicosis. In the 35 live births, there were six cases of neonatal Graves' disease, all of whom had a TSHR-Ab level above 500 percent of normal; in addition, six other babies with a TSHR-Ab above 500 percent of normal did not develop hyperthyroidism. In this study, measurement of the TSHR-Ab had a 100 percent sensitivity, with 50 percent specificity. The incidence of neonatal Graves' disease in this study was 17 percent, which is a higher rate than previously reported [8].

PATHOGENESIS — Neonatal (and fetal) Graves' hyperthyroidism results from the transplacental passage of maternal stimulatory thyrotropin receptor antibody (TSHR-Ab) [3,9,10]. In a systematic review, the lowest level of maternal TSHR-Ab leading to neonatal Graves' disease was 4.4 U/L, which corresponded to 3.7 times the upper limit of normal [11]. Most neonatal Graves' disease occurs in the setting of active Graves' hyperthyroidism in the mother, though it has also been reported in a baby born to a woman with a stimulatory TSHR-Ab associated with Hashimoto thyroiditis [12]. Importantly, the disorder also can occur in infants of women with a history of Graves' hyperthyroidism treated with thyroidectomy or radioactive iodine in the past [13]. After a woman with Graves' disease undergoes one of these treatments, the risk of having an infant affected by neonatal Graves' disease falls over time, in conjunction with decreases in TSHR-Ab levels. The risk of neonatal Graves' disease is low five years after radioactive iodine, but some mothers still have persistent TSHR-Ab elevation and will deliver babies with neonatal Graves' disease [14]. A study of the time course of decrease in TSHR-Ab after total thyroidectomy reported that the median TSHR-Ab half-life was 93.5 days, though it was longer in patients with Graves' ophthalmopathy and/or those who smoked (162.5 days for one of these risk factors and 357.4 days for those with both) [15]. As described above, measurement of maternal serum TSHR-Ab in the third trimester may be helpful in predicting whether a newborn will be affected. (See "Hyperthyroidism during pregnancy: Treatment".)

Serial in utero ultrasonography with measurement of fetal thyroid size has also been reported to help determine which neonates are likely to manifest neonatal hyperthyroidism [16]. In a report of 20 pregnant women with Graves' disease treated with an antithyroid drug, the fetal thyroid gland was enlarged in five pregnancies. In these five patients, the maternal antithyroid medication dose was decreased resulting in a reduction of the fetal thyroid gland to a normal size in three cases but in the other two cases the gland remained enlarged. These latter two infants both developed neonatal Graves' disease [16]. Thus, care must be taken because fetal goiter may be a feature of in utero hypothyroidism or hyperthyroidism. Another study using ultrasonography reported that a hyperthyroid fetus was more likely to have a goiter with central vascularization, along with other findings, including fetal tachycardia, increased fetal movement, and advanced bone maturity [17].

Given the pathogenesis, one would expect twins to be equally affected. However, in a single case report, one twin was hyperthyroid and the other was hypothyroid [18]. Both eventually recovered to a euthyroid state.

Natural history — Neonatal Graves' hyperthyroidism resolves spontaneously in 3 to 12 weeks as the maternal TSHR-Ab is metabolized and disappears from the infant's circulation.

Other causes of neonatal hyperthyroidism — Rarely, neonatal hyperthyroidism may be caused by genetic defects of the thyroid-stimulating hormone (TSH) receptor or its mediators; these forms are not associated with maternal Graves' disease.

Thyrotropin-receptor activating mutations — Activating germline mutations of the TSH receptor are a rare cause of neonatal hyperthyroidism [19-22]. Neither the infant nor the mother has circulating TSHR-Ab or evidence for autoimmune thyroid disease. This condition is inherited as an autosomal dominant trait and there may be a family history of hyperthyroidism.

In contrast with neonatal Graves' hyperthyroidism, this form of hyperthyroidism persists indefinitely and will recur whenever antithyroid drug treatment is discontinued. Thus, treatment with either surgery or radioactive iodine (in children >10 years of age) is indicated eventually.

Alpha subunit G protein-activating mutation (McCune-Albright syndrome) — Another rare cause of neonatal hyperthyroidism is an activating mutation of the alpha subunit of the G protein that stimulates adenylate cyclase [23-25]. This typically occurs as part of the McCune-Albright syndrome. As with thyrotropin-receptor activating mutations, neither mother nor infant has TSHR-Ab. In contrast with thyrotropin-receptor activating mutations, however, these are somatic cell mutations, and so this is a sporadic disorder.

This form of hyperthyroidism will persist indefinitely, and so surgery or radioactive iodine treatment (in children >10 years of age) is indicated eventually.

CLINICAL MANIFESTATIONS — The clinical manifestations of hyperthyroidism in neonates are those of hyperthyroidism in general plus some features unique to neonates. The characteristic abnormalities are (picture 1):

- Low birth weight for gestational age (intrauterine growth restriction) [26]
- Premature birth
- Microcephaly (may be a manifestation of accelerated brain development with premature completion of neuronal morphogenesis)
- Frontal bossing and triangular facies
- Warm, moist skin
- Irritability, hyperactivity, restlessness, and poor sleep
- Tachycardia with a bounding pulse, and sometimes cardiomegaly, cardiac arrhythmias, or heart failure
- Persistent pulmonary hypertension (rare)
- Fetal hydrops (uncommon)

- Hyperphagia, but poor weight gain, and increased frequency of bowel movements
- Hepatosplenomegaly
- Diffuse goiter, usually small, but occasionally large enough to cause compression of the airway
- Stare and occasionally exophthalmos (presumably true Graves' ophthalmopathy)

Timing of symptoms — The time of onset and severity of symptoms are variable, depending upon whether the mother is taking an antithyroid drug at the time of delivery. Infants born to mothers not receiving an antithyroid drug, including mothers who are euthyroid as a result of previous ablative treatment for Graves' hyperthyroidism, are hyperthyroid at the time of birth. Infants of mothers taking an antithyroid drug may be euthyroid or even hypothyroid at birth, and become hyperthyroid as the antithyroid drug is metabolized and excreted by 7 to 10 days after delivery [27]. In these cases, early clinical manifestations of hyperthyroidism are apparent by three to five days of age. In a report of six infants born to mothers with Graves' disease treated with antithyroid drugs during pregnancy, symptoms and signs of congenital hyperthyroidism developed between days 10 and 20 of life [28]. In a larger study of 96 neonates born to mothers with Graves' disease, most had a "subclinical" course with high serum free T4 levels peaking at five days of age; after 14 days of age, free T4 levels normalized, although serum TSH remained suppressed for up to three months [29].

EVALUATION — A summary of the pathways to diagnosis is presented in the algorithm (algorithm 1), which reflects recommendations in a literature-based review [30]. The steps in diagnosing neonatal Graves' disease depend on how the infant comes to medical attention.

Maternal Graves' disease during pregnancy — Many cases of neonatal Graves' disease are suspected based on a history of maternal Graves' disease and are recognized during pregnancy. In such cases, we suggest the following sequence of laboratory tests:

Prenatal testing — Measurement of maternal serum thyrotropin receptor antibody (TSHR-Ab) during the third trimester helps to predict which infants are at higher risk for development of fetal and neonatal Graves' hyperthyroidism. The most accurate TSHR-Ab test is a measurement of thyroid-stimulating immunoglobulin (TSI). TSI is a functional assay, measuring production of cyclic adenosine monophosphate (AMP) in cultured thyroid follicular cells, confirming the presence of a stimulating antibody. An alternative TSHR-Ab test is measurement of thyrotropin receptor antibody (TR-Ab). This test, employing competitive protein binding methodology, shows that there is an antibody that competes with TSH binding to its receptor, but it does not provide information about whether it is a stimulating or blocking antibody. Although TR-Ab assays do not indicate biologic activity, women with Graves' disease usually have stimulatory antibodies. As noted above, the fetus or infant is more likely to have Graves' hyperthyroidism when the maternal TSHR-Ab value is more than 500 percent of normal values [5,31].

- If the maternal TSHR-Ab is positive, the infant is at risk for developing neonatal Graves' disease, particularly if the value is greater than 500 percent of normal. In this case, the infant should be evaluated at birth and during the first few weeks of life, as outlined below.
- If a mother with positive TSHR-Ab has active Graves' disease and is treated with an antithyroid drug during pregnancy, the newborn most likely will have transient hypothyroidism after birth.
- If the maternal TSHR-Ab is negative, neonatal Graves' disease is unlikely; these cases can be followed clinically, with measurement of thyroid function only if symptoms or signs of hyperthyroidism develop.

Cord blood — Measurement of TSHR-Ab in cord blood is not essential for the diagnosis but helps to predict the risk of neonatal Graves' disease in the infant. In a report of 68 pregnant women with a history of Graves' disease, 33 had positive TSHR-Ab. Of those with positive TSHR-Ab, 73 percent (27 of 33) had infants with positive TSHR-Ab on cord blood assays, and 26 percent (7 of 27) of those infants went on to develop neonatal Graves' disease [32]. None of the 35 babies born to mothers with negative TSHR-Ab developed Graves' disease. In babies born to a mother with known positive TSHR-Ab, and so likely treated with an antithyroid drug, measurement of thyroid function tests (free thyroxine [fT4] and thyroid-stimulating hormone [TSH]) in cord blood is not helpful because these results do not predict the risk of neonatal hyperthyroidism [30].

Testing of the neonate — For infants born to mothers with a history of Graves' disease but in whom the maternal TSHR-Ab status is unknown, thyroid function should be assessed by measuring serum fT4, total triiodothyronine (T3), and TSH at delivery or soon thereafter. If the mother has a significantly elevated stimulatory TSHR-Ab level and was not treated with an antithyroid drug during pregnancy, hyperthyroidism will be present in the infant on initial testing. In cases where the mother was treated with an antithyroid drug up to delivery, thyroid function tests in the first day of life are normal or may even show hypothyroidism.

Thyroid function tests should be repeated at three to five days of life and again at 10 to 14 days of life; in the report cited above, a rising fT4 and free T3 during the first postnatal week predicted the development of hyperthyroidism [32]. The results are interpreted as follows (algorithm 1):

- Infants with biochemical evidence of hyperthyroidism (elevated fT4 and total T3, and low TSH) at any of these time points have neonatal Graves' disease and should be treated until the disease resolves. (See 'Diagnosis' below and 'Treatment' below.)

- Infants with biochemical evidence of **HYPO**thyroidism (low fT4 and total T3, with high TSH) should be reevaluated one week later and then serially until thyroid function is stably normal, or to determine if hypothyroidism will persist. In the majority of cases, the hypothyroidism is due to maternal antithyroid drug treatment and will resolve by two weeks of age; no treatment is necessary in these cases. Hypothyroidism persisting longer than two weeks likely is caused by maternal TSHR-Ab, now a blocking antibody. (See "Clinical features and detection of congenital hypothyroidism", section on 'Transient congenital hypothyroidism'.)

  A rare infant may evolve from hypothyroidism to hyperthyroidism, as the balance of TSHR-Ab switches from a blocking to a stimulating antibody.

  Some infants may develop **central** hypothyroidism (manifested by low fT4 and **low** TSH) as neonatal Graves' disease resolves, typically between 3 and 12 weeks of age. This type of hypothyroidism also may be transient.

  Treatment depends on the duration and type of the hypothyroidism. (See 'Hypothyroidism (transient)' below.)

- Infants with normal results at all of these time points should be followed clinically, with repeat measurements of thyroid function tests if symptoms develop.

Infants coming to attention after birth — Some infants come to medical attention after birth for one of the following reasons:

- Maternal Graves' disease was not recognized until after birth (mother not previously diagnosed, or her diagnosis was not known during labor and delivery).

- An infant comes to medical attention because of symptoms suggesting neonatal Graves' disease, which may include low birth weight, microcephaly, irritability, and tachycardia. (See 'Clinical manifestations' above.)

- Routine newborn screening identifies elevated T4 in an infant [33]. This scenario is uncommon because most newborn screening programs in the United States and worldwide undertake an initial TSH test and so would not identify a baby with an elevated T4. Some programs employ a T4-reflex TSH test approach, or combined T4 and TSH test approach, and have the potential to identify a baby with an elevated T4, but only a few programs actually follow-up such cases.

In any of these scenarios, thyroid function tests should be performed in the infant as soon as this issue is recognized, then repeated at three to five days of age, and again at 10 to 14 days of age (algorithm 1) [30]. Results of the maternal TSHR-Ab tests, if available, are not critical to management but may be helpful to estimate the infant's risk of developing neonatal Graves' disease. (See 'Testing of the neonate' above.)

DIAGNOSIS

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Neonatal Graves' disease – Neonatal Graves' disease is diagnosed in a newborn infant with elevated free T4 (fT4) and total triiodothyronine (T3), and low thyroid-stimulating hormone (TSH). These values should be interpreted in the context of the infant's age because the normal range for these values is higher during the first few days and weeks of life compared with values in older infants (table 1) (see "Thyroid physiology and screening in preterm infants"). Once the diagnosis of neonatal Graves' disease is made, treatment should be initiated, as outlined below. (See 'Neonatal Graves' disease' below.)

- **Transient hypothyroidism** – Other infants will have neonatal primary HYPOthyroidism, indicated by low fT4 and total T3 and elevated TSH. The hypothyroidism usually is transient, caused by maternal antithyroid drug treatment or maternal thyrotropin receptor (TSHR)-blocking antibodies, and the infant may become euthyroid or hyperthyroid (neonatal Graves' disease) any time during the first few weeks of life. Occasionally, infants develop transient **central** hypothyroidism, manifested by low fT4 and **low** TSH, as neonatal Graves' disease resolves (typically between 3 and 12 weeks of age) (see 'Testing of the neonate' above). Treatment depends on the type and duration of the hypothyroidism. (See 'Hypothyroidism (transient)' below.)

TREATMENT

Neonatal Graves' disease — Once neonatal Graves' disease is confirmed by clinical and biochemical evaluation, treatment should be initiated promptly. Before beginning treatment, we recommend measuring total triiodothyronine (T3) concentration in addition to free thyroxine (fT4) and thyroid-stimulating hormone (TSH), to use as a "baseline" when monitoring treatment with methimazole. With methimazole treatment, often the free fT4 is low-normal and the total T3 is high-normal, such that both are needed for accurate methimazole dose adjustments.

Therapy should consist of the following:

- Administration of methimazole and a beta-adrenergic blocker:
  - The antithyroid drug, methimazole (MMI; 0.25 to 1.0 mg/kg per day), should be administered every eight hours (see "Thionamides in the treatment of Graves' disease"). Propylthiouracil is also effective but has more frequent and severe side effects, including a risk of hepatotoxicity [34]. Because of these safety concerns, the Endocrine Society, the American Thyroid Association, and the US Food and Drug Administration recommend **against** the use of propylthiouracil (PTU) as first-line treatment for Graves' disease throughout childhood [35-37].
  - A beta-adrenergic blocker, such as propranolol (2 mg/kg per day every eight hours), is an important adjunct in controlling neuromuscular and cardiovascular hyperactivity. A potential advantage of propranolol is inhibition of T4 conversion to T3. If a more cardio-specific beta blocker is preferred, atenolol (1 mg/kg daily) can be used. (See "Beta blockers in the treatment of hyperthyroidism".)

  In most cases, the above combination will control the hyperthyroidism within a few weeks and is sufficient treatment.

- Iodine may be added for neonates whose hyperthyroidism is not controlled with MMI and a beta-adrenergic blocker. Some clinicians prefer to routinely use iodine instead of the MMI/beta-adrenergic blocker, at the following dose:
  - Iodine, in the form of one drop (8 mg) of Lugol's solution (126 mg iodine/mL) every eight hours orally or SSKI (potassium iodide) one to two drops daily, can be given to inhibit thyroid hormone release. Iodine, if added, is generally used for only one to two weeks. (See "Iodine in the treatment of hyperthyroidism".)

- Glucocorticoids can also be given in extremely ill infants. In addition to their antiinflammatory actions, glucocorticoids inhibit thyroid hormone secretion and decrease peripheral conversion of thyroxine (T4) to T3. Digoxin may be helpful if heart failure is present.

Once improvement is evident, treatment should be gradually decreased and then discontinued. This may require frequent (ie, weekly) monitoring of thyroid function tests to allow adjustment of the antithyroid drug dose to

maintain normal serum free T4 and T3 levels. As noted above, neonatal Graves' hyperthyroidism usually resolves spontaneously between 3 and 12 weeks of life, although it can persist for six months or even longer.

Hypothyroidism (transient) — For infants with **primary** hypothyroidism (indicated by low fT4 and total T3 and elevated thyroid-stimulating hormone [TSH]), this is usually due to maternal antithyroid drug treatment and will resolve by two weeks of age; no treatment is necessary in these cases. If the hypothyroidism persists beyond two weeks of age, as occurs with a thyrotropin receptor (TSHR)-blocking antibody, then levothyroxine treatment should be started. In these cases, we recommend following the management guidelines as for infants with congenital hypothyroidism (see "Treatment and prognosis of congenital hypothyroidism"). Such cases are usually transient; measurement of the infant's TSHR-blocking antibody will provide guidance as to when it is safe to discontinue levothyroxine. If it is unclear whether the infant has recovered to euthyroidism, we recommend treating until age two years, followed by a trial off treatment and measurement of serum free T4 and TSH four weeks later.

Infants who develop **central** hypothyroidism (manifested by low fT4 and **low** [or "inappropriately normal"] TSH) as neonatal Graves' disease resolves (typically between 3 and 12 weeks of age), should be treated with levothyroxine until it resolves. (See "Clinical features and detection of congenital hypothyroidism", section on 'Transient congenital hypothyroidism' and "Treatment and prognosis of congenital hypothyroidism".)

PROGNOSIS — With adequate therapy, initiated promptly, most neonates with hyperthyroidism improve rapidly. Nevertheless, some of these patients have intelligence quotients (IQs) in the 80s when measured at school age, even if they were treated promptly for hyperthyroidism during the neonatal period. These observations suggest that fetal or neonatal hyperthyroidism has adverse effects on the developing nervous system. Growth retardation, craniosynostosis, hyperactivity, and developmental and behavioral problems have been described as long-term sequelae of neonatal Graves' hyperthyroidism; the relationship between these findings and the adequacy of treatment is uncertain [38].

A few infants with neonatal Graves' hyperthyroidism later have diminished thyroid-stimulating hormone (TSH) secretion, which may result in central hypothyroidism [39]. This is thought to be secondary to prenatal exposure of the hypothalamus and pituitary to high serum thyroid hormone concentrations during a critical stage of development. Although the neonatal Graves' disease usually is transient, there is evidence that insufficient antithyroid drug treatment during pregnancy increases the risk of permanent central hypothyroidism, drawing attention to the importance of careful monitoring of maternal thyroid function and appropriate antithyroid drug dosing during pregnancy [40]. There is also evidence that decreased TSH secretion might impair normal fetal thyroid gland development, in a process described as thyroid "disintegration" [41].

FETAL HYPERTHYROIDISM — High maternal serum thyrotropin receptor antibody (TSHR-Ab) concentrations may cause fetal hyperthyroidism. It is characterized by fetal hyperactivity, tachycardia (>160 beats/min) after 22 weeks gestation, advanced bone maturation, and a goiter. If these abnormalities are present, corrective therapy (eg, cautious administration of an antithyroid drug to the mother) may be indicated [42]. Besides the untoward hypermetabolic effects, fetal hyperthyroidism may accelerate fetal central nervous system maturation, causing disorganization of brain development and, therefore, intellectual disability (mental retardation). The diagnosis and treatment of fetal hyperthyroidism are discussed elsewhere in the program. (See "Hyperthyroidism during pregnancy: Treatment", section on 'Fetal or neonatal hyperthyroidism'.)

Maternal antithyroid drug treatment may also result in fetal goiter and hypothyroidism. Such cases may be managed by decreasing the maternal antithyroid dose (if this can be done safely), or by intra-amniotic injections of thyroid hormone [43,44]. (See "Hyperthyroidism during pregnancy: Treatment", section on 'Fetal or neonatal hyperthyroidism'.)

SUMMARY AND RECOMMENDATIONS

- Neonatal Graves' disease develops in about 1 to 5 percent of infants born to mothers with Graves' hyperthyroidism and is caused by the transplacental passage of maternal stimulatory thyrotropin-receptor antibodies (TSHR-Ab). In babies who are exposed to high titers of TSHR-Ab, hyperthyroid symptoms typically present at birth but the infant may also have hypothyroidism following delivery, depending on the balance of the maternal stimulatory TSHR-Ab and maternal antithyroid drug (if given). Neonatal Graves'

hyperthyroidism resolves spontaneously within 3 to 12 weeks after birth as the maternal TSHR-Ab disappears from the infant's circulation. (See 'Incidence' above and 'Pathogenesis' above.)

- The clinical manifestations of hyperthyroidism in neonates include premature birth and/or low birth weight for gestational age, microcephaly, irritability, hyperactivity, tachycardia and arrhythmias, hyperphagia, increased frequency of bowel movements, hepatosplenomegaly, goiter, and stare (picture 1). The time of onset and severity of symptoms are variable, depending upon whether the mother is taking an antithyroid drug at the time of delivery. (See 'Clinical manifestations' above.)
- To estimate the risk of neonatal Graves' disease in infants born to mothers with a history of Graves' disease, maternal serum TSHR-Ab should be measured during the third trimester. Neonatal hyperthyroidism is most likely when the TSHR-Ab activity of maternal serum is above 500 percent of the values in serum of normal subjects. (See 'Prenatal testing' above.)
- High maternal serum TSHR-Ab concentrations may cause fetal hyperthyroidism, which is characterized by fetal hyperactivity, tachycardia after 22 weeks gestation, advanced bone maturation, and a goiter. If these abnormalities are present, corrective therapy (administration of an antithyroid drug to the mother) may be indicated because fetal hyperthyroidism may cause untoward effects, particularly on the cardiovascular system, and may also disrupt fetal central nervous system development. (See 'Fetal hyperthyroidism' above.)
- In cases in which the history of maternal Graves' disease is known at birth, we recommend measurement of TSHR-Ab in the cord blood, as this result can predict the risk of neonatal Graves' disease. Neonates with negative TSHR-Ab in cord blood are unlikely to develop Graves' disease; they can be followed clinically, with a check of thyroid function tests only if symptoms or signs of hyperthyroidism develop. (See 'Cord blood' above.)
- All infants born to mothers with a history of Graves' disease and whose cord blood TSHR-Ab status is unknown should be assessed by measuring serum free thyroxine (fT4), total triiodothyronine (T3), and thyroid-stimulating hormone (TSH) at birth (or soon thereafter), and again at three to five days of age and 10 to 14 days of age (algorithm 1). This includes infants whose mothers are euthyroid as a result of previous ablative treatment for Graves' hyperthyroidism. It is important to remember the normal range for both serum free T4, total T3, and TSH concentrations is higher in the first few days and weeks of life than in older children and adults. (See 'Evaluation' above and "Thyroid physiology and screening in preterm infants".)
- If neonatal hyperthyroidism is confirmed by clinical and biochemical evaluation, treatment should be initiated promptly. We recommend that these infants be treated with a combination of the antithyroid drug methimazole and a beta-adrenergic blocker such as propranolol or atenolol, rather than no treatment or monotherapy (**Grade 1B**). Iodine can be given to inhibit thyroid hormone release; iodine is generally reserved for neonates whose hyperthyroidism is not controlled with an antithyroid drug and beta blocker. (See 'Treatment' above.)
- Some infants born to mothers with Graves' disease develop transient HYPOthyroidism, which is caused by maternal antithyroid drug treatment or maternal TSHR-blocking antibodies. Other infants develop central hypothyroidism as neonatal Graves' disease resolves. Treatment depends on the type and duration of the hypothyroidism. (See 'Hypothyroidism (transient)' above.)
- With adequate therapy, most neonates with hyperthyroidism improve rapidly and can be weaned from medication by 3 to 12 weeks of age. Nevertheless, there may be some long-term adverse effects on cognitive development even with prompt treatment. Some individuals later develop central hypothyroidism due to prenatal exposure of the hypothalamus and pituitary to high serum thyroid hormone concentrations. (See 'Prognosis' above.)

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Topic 5839 Version 13.0

GRAPHICS

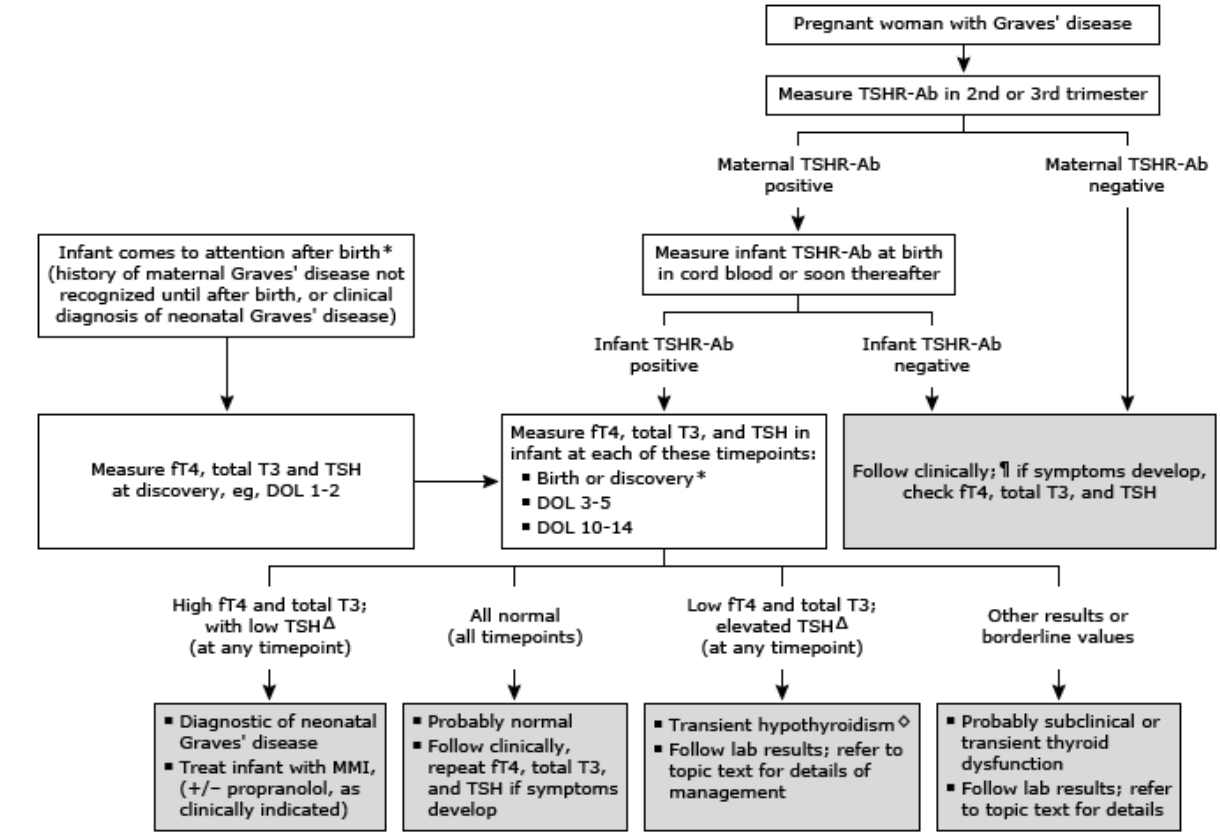
Neonatal hyperthyroidism

These twins demonstrate clinical features of neonatal hyperthyroidism (thyrotoxicosis), including an anxious-appearing stare and diminished subcutaneous fat.

Courtesy of Dr. Stephen LaFranchi.

Graphic 95959 Version 1.0

Evaluation and management of infants at risk for neonatal Graves' disease



TSHR-Ab: thyroid stimulating hormone receptor antibodies; fT4: free thyroxine; T3: triiodothyronine; TSH: thyroid stimulating hormone; DOL: day of life; MMI: methimazole.

* For infants coming to medical attention after birth, thyroid function tests are performed as soon as the possibility of neonatal Graves' disease is recognized, and repeated during the first two weeks of life, as shown. Results of maternal TSHR-Ab tests, if available, may be helpful to estimate the infant's risk of developing neonatal Graves' disease.

¶ Follow-up is recommended because some TSH-R antibody tests may have false-negative results.

Δ Thyroid function tests should be interpreted in the context of the infant's age because the normal values for these tests are higher during the first few weeks of life compared with values in older infants (refer to UpToDate topic text for details).

◇ In most of these infants, the hypothyroidism is transient, and is due to maternal antithyroid drug treatments, although some cases are caused by maternal TSH-R blocking antibodies. The infant may become euthyroid or hyperthyroid anytime during the first few weeks of life. As neonatal Graves' disease resolves, some infants may develop **central** hypothyroidism (low fT4 and low TSH). Central hypothyroidism also may be transient, but should be treated with levothyroxine until the hypothyroidism resolves.

Graphic 108929 Version 2.0

Concentrations of free T4, T4, T3, and TSH in preterm and term infants, in cord blood at birth and at 7, 14, and 28 days of age (mean ± 1 SD)

Gestation (weeks)	Age of infant	Free T4 (ng/dL)	T4 (microgram/dL)	T3 (ng/dL)	TSH (mU/L)
23-27 weeks	Cord	1.28 ± 0.4	5.4 ± 2.0	20 ± 15	6.8 ± 2.9
	7 d	1.47 ± 0.6	4.0 ± 1.8	33 ± 20	3.5 ± 2.6
	14 d	1.45 ± 0.5	4.7 ± 2.6	41 ± 25	3.9 ± 2.7
	28 d	1.50 ± 0.4	6.1 ± 2.3	63 ± 27	3.8 ± 4.7
28-30 weeks	Cord	1.45 ± 0.4	6.3 ± 2.0	29 ± 21	7.0 ± 3.7
	7 d	1.82 ± 0.7	6.3 ± 2.1	56 ± 24	3.6 ± 2.5
	14 d	1.65 ± 0.4	6.6 ± 2.3	72 ± 28	4.9 ± 11.2
	28 d	1.71 ± 0.4	7.5 ± 2.3	87 ± 31	3.6 ± 2.5
31-34 weeks	Cord	1.49 ± 0.3	7.6 ± 2.3	35 ± 23	7.9 ± 5.2
	7 d	2.14 ± 0.6	9.4 ± 3.4	92 ± 36	3.6 ± 4.8
	14 d	1.98 ± 0.4	9.1 ± 3.6	110 ± 41	3.8 ± 9.3
	28 d	1.88 ± 0.5	8.9 ± 3.0	120 ± 40	3.5 ± 3.4
≥37 weeks	Cord	1.41 ± 0.3	9.2 ± 1.9	60 ± 35	6.7 ± 4.8
	7 d	2.70 ± 0.6	12.7 ± 2.9	148 ± 50	2.6 ± 1.8
	14 d	2.03 ± 0.3	10.7 ± 1.4	167 ± 31	2.5 ± 2.0
	28 d	1.65 ± 0.3	9.7 ± 2.2	176 ± 32	1.8 ± 0.9

T4: thyroxine; T3: triiodothyronine; TSH: thyroid stimulating hormone; SD: standard deviation.

Adapted with permission from: Williams FL, Simpson J, Delahunty C, et al. Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. J Clin Endocrinol Metab 2004; 89:5314.

Graphic 72215 Version 7.0

Contributor Disclosures

Stephen LaFranchi, MD Nothing to disclose **Mitchell E Geffner, MD** Consultant/Advisory Boards: Daiichi-Sankyo [Type 2 diabetes (Colesevelam)]; NovoNordisk [Growth (Somatropin)]; Nutritional Growth Solutions [Growth]; Pfizer [Growth (Somatropin)]. Spruce Biosciences [congenital adrenal hyperplasia]. Other Financial Interest: McGraw-Hill [Pediatric endocrinology (Textbook royalties)]. **Alison G Hoppin, MD** Nothing to disclose

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Conflict of interest policy