Neonatal Thyrotoxicosis

Stephanie L. Samuels, MDa, Sisi M. Namoc, MDb,
Andrew J. Bauer, MDc,*
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INTRODUCCIÓN

La tirotoxicosis neonatal (hipertiroidismo) es menos frecuente que el hipotiroidismo congénito; sin embargo, puede llevar a una morbilidad y mortalidad significativas si no es oportunamente reconocida y tratada adecuadamente. La mayoría de los casos son transitorios, secundarios a la madre portadora de hipertiroidismo autoinmune (enfermedad de Graves [EG]). El hipertiroidismo neonatal puede también ocurrir secundariamente a la activación de mutaciones en el receptor de la hormona estimulante de la tiroides (TSHR) o mutaciones activadoras en la subunidad alfa estimuladora de la guanina, nucleótido unido a la proteína de un gen (GNAS) en el Síndrome de McCune-Albright (Tabla 1). Este artículo resume las recomendaciones actuales para detección y manejo de hipertiroidismo en los períodos fetal y neonatal, con un enfoque en tirotoxicosis neonatal secundaria a EG materna. El monitoreo temprano y el tratamiento son cruciales para optimizar los resultados a corto y largo plazo del paciente.

Le invitamos a leer el texto completo de ésta publicación en ingles.

Neonatal Thyrotoxicosis

Stephanie L. Samuels, MD[a], Sisi M. Namoc, MD[b], Andrew J. Bauer, MD[c,*]

KEYWORDS

• Neonatal • Fetal • Thyrotoxicosis • Hyperthyroidism • Graves disease

KEY POINTS

- Neonatal thyrotoxicosis is most commonly caused by autoimmune hyperthyroidism, which results from transplacental passage of thyroid-stimulating hormone receptor–stimulating immunoglobulins from mother to fetus in the setting of maternal Graves disease.
- Pregnant women with current or past history of hyperthyroidism require screening to determine whether the fetus/neonate is at increased risk to develop hyperthyroidism.
- Nonautoimmune genetic causes of hyperthyroidism should be suspected in cases of neonatal thyrotoxicosis when there is no maternal history of Graves disease.
- Neonates with symptomatic hyperthyroidism require prompt initiation of therapy and close monitoring of response in consultation with a pediatric endocrinologist.

INTRODUCTION

Neonatal thyrotoxicosis (hyperthyroidism) is less prevalent than congenital hypothyroidism; however, it can lead to significant morbidity and mortality if not promptly recognized and adequately treated. Most cases are transient, secondary to maternal autoimmune hyperthyroidism (Graves disease [GD]). Neonatal hyperthyroidism can also occur secondary to activating mutations in the thyroid-stimulating hormone receptor (TSHR) or activating mutations in the stimulatory alpha subunit of the guanine nucleotide-binding protein (*GNAS*) gene in McCune-Albright (**Table 1**).

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[a] Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA; [b] National Institute of Child Health, 600 Brasil Avenue, Breña - Lima 05, Peru; [c] Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, The Thyroid Center, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA
* Corresponding author.
E-mail address: bauera@chop.edu

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Table 1
Causes of neonatal hyperthyroidism

Cause	Cause	Expected Course
Autoimmune hyperthyroidism (neonatal GD)	Transplacental passage of TRAb from mother to fetus	Transient (generally resolves in 4–5 mo after TRAb clearance)
Nonautoimmune hyperthyroidism	• Activating mutation in the TSH receptor (autosomal dominant) • Activating mutation in *GNAS* (McCune-Albright syndrome)	Permanent (persists after the neonatal period)

Abbreviation: TRAb, TSH receptor–stimulating antibodies.

This article summarizes current recommendations for screening and management of hyperthyroidism in both the fetal and neonatal periods, with a focus on neonatal thyrotoxicosis secondary to maternal GD. Early monitoring and treatment are crucial for optimizing short-term and long-term patient outcomes.

PATHOGENESIS OF NEONATAL HYPERTHYROIDISM

Neonatal Graves Disease

Neonatal GD is caused by transplacental passage of maternal stimulating TSHR antibodies (TRAb), leading to unregulated activation of the TSHR and overproduction of thyroid hormone. The prevalence of GD in pregnant women has been estimated to be about 0.1% to 0.4%, and studies have shown that approximately 1% to 5% of neonates born to mothers with GD develop hyperthyroidism.[1–3] Therefore, neonatal GD is expected to occur in 1 in 25,000 to 1 in 50,000 newborns. However, the incidence of neonatal GD may be higher if cases of asymptomatic biochemical hyperthyroidism are included.[4] Unlike GD in older children and adolescents, which disproportionately affects girls compared with boys, neonatal GD occurs in male and female infants equally.

Neonates of mothers with GD are at increased risk for neonatal GD, but hypothyroidism can also occur (**Fig. 1**). There are 2 types of TRAb: TSHR-stimulating immunoglobulins (TSI), which cause overproduction of thyroid hormone (hyperthyroidism), and TSHR inhibitory (blocking) immunoglobulins, which can cause hypothyroidism. Fetal thyroid hormone synthesis begins at approximately 10 to 12 weeks' gestation, and the fetal TSHR starts responding to stimulation, including stimulation by TSI, during the second trimester.[1] TRAb, which belong to the immunoglobulin G (IgG) class, freely cross the placenta, as does iodine, some thyroxine (T4), and any antithyroid drugs (ATDs) the mother may be taking for the treatment of GD. The balance of stimulatory and inhibitory TRAb, as well as ATD dose, influences the thyroid status in the fetus and neonate and the fluctuation of maternal antithyroid antibody titers may result in different risks to the fetus or neonate. One illustrative case report described a woman with GD whose 3 successive offspring had different outcomes: the first was euthyroid, the second developed transient hyperthyroidism, and the third was hypothyroid at birth.[5] In cases of neonatal GD, maternal TRAb typically clear from the infant's circulation by 4 to 6 months of age, with resultant resolution of hyperthyroidism.[1]

Other Causes

Nonautoimmune causes of neonatal hyperthyroidism, which are generally permanent rather than transient, have also been described. Genetic mutations causing constitutive activation of the *TSHR* are either inherited in an autosomal dominant manner or

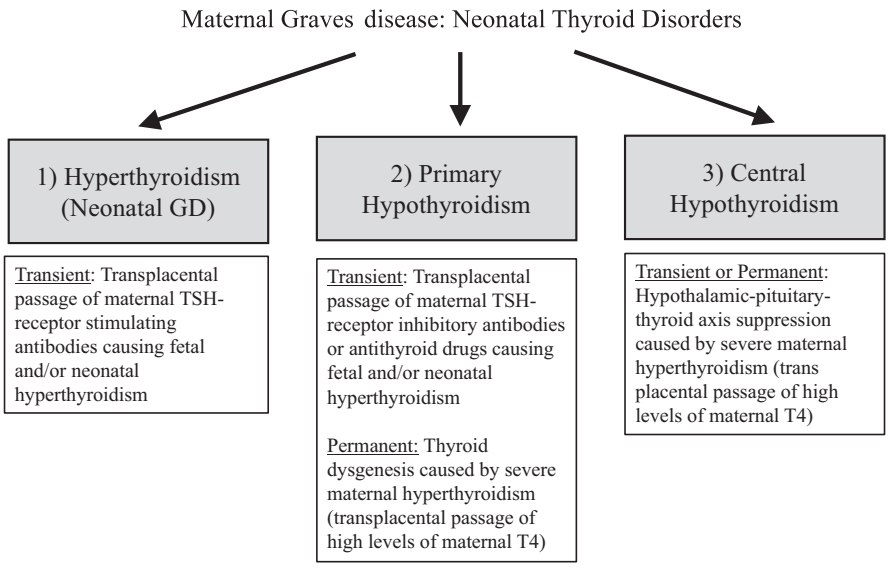

Fig. 1. Neonatal thyroid disorders in neonates of mothers with GD. T4, thyroxine.

may occur de novo, and lead to hyperthyroidism that may present during or after the neonatal period.[6,7] In McCune-Albright syndrome, activating mutations in *GNAS*, the gene encoding the alpha subunit of stimulatory G proteins, can also cause neonatal hyperthyroidism.[8] These genetic causes of neonatal hyperthyroidism should be considered in cases of neonatal thyrotoxicosis when there is no apparent maternal history of autoimmune hyperthyroidism.

Although iodine overload during pregnancy and during the neonatal period has frequently been associated with hypothyroidism, there is a theoretic potential for hyperthyroidism. Rare cases of thyrotoxicosis in a neonate following exposure to topical iodine have been reported.[9]

NEONATAL HYPERTHYROIDISM: FETAL ASPECTS

Manifestations of Hyperthyroidism in the Fetus

Signs of hyperthyroidism can be detected in the fetus, and, if present, are highly predictive of neonatal hyperthyroidism (**Box 1**). Particularly in cases in which maternal GD is poorly controlled, features concerning for fetal hyperthyroidism include fetal tachycardia (heart rate >160 beats/min), thyroid enlargement (goiter; fetal neck circumference >95%), intrauterine growth retardation, polyhydramnios or oligohydramnios, advanced bone age, craniosynostosis with microcephaly, and hydrops.[2,10] Polyhydramnios is typically associated with a goiter with resultant esophageal and/or tracheal obstruction. Fetal bone age is assessed at the distal femur, because the distal femoral epiphysis becomes detectable at about 32 weeks' gestation.[11] An advanced bone age is present if the femoral epiphysis is present before the 31st gestational week. For patients with severe thyrotoxicosis, there is an increased risk for premature delivery, and, at the extreme, fetal death may occur.[1]

Screening During Pregnancy

Recent consensus guidelines from the American Thyroid Association and Endocrine Society recommend determining maternal TRAb levels between 20 and 24 weeks'

Box 1
Manifestations of fetal and neonatal hyperthyroidism

Clinical manifestations of fetal hyperthyroidism:
- Tachycardia
- Goiter
- Intrauterine growth retardation
- Oligohydramnios
- Advanced bone maturation
- Prematurity
- Fetal death

Clinical manifestations of neonatal hyperthyroidism:
- Hemodynamic instability (tachycardia, hypertension, tachypnea/respiratory distress, hyperthermia)
- Irritability, sleep difficulty, hyperexcitability
- Increased appetite, feeding difficulties
- Poor weight gain or weight loss
- Diarrhea
- Flushing/sweating
- Stare and/or eyelid retardation
- Small fontanelle
- Craniosynostosis, microcephaly
- Severe cases: hepatosplenomegaly, thrombocytopenia, jaundice, pulmonary hypertension, cardiac failure, death

gestation.[12,13] All pregnant women with a history of GD, even those with hypothyroidism following definitive therapy with radioiodine ablation (RAI; ^{131}I) or total thyroidectomy, should undergo screening because increased TRAb levels can persist for years after definitive therapy. In a randomized controlled trial with 5-year follow-up, patients with newly diagnosed GD were randomized to receive medical therapy, thyroid surgery, or ^{131}I therapy. Medical therapy and surgery led to a disappearance of TRAb in 70% to 80% of patients after 18 months. In contrast, radioiodine (RAI) therapy led to increased TRAb levels over the first year following treatment and disappearance of TRAb was much less frequent, even years after RAI treatment.[14] Thus, all pregnant women taking thyroid hormone therapy for hypothyroidism should be asked whether they have a prior history of GD in order to determine which women should have TRAb testing in addition to the usual thyroid surveillance necessary to optimize levothyroxine therapy.

Pregnancies complicated by increased maternal TRAb levels are associated with a higher risk for development of fetal and neonatal hyperthyroidism. The risk increases markedly if maternal TRAb level is increased more than 2 to 3 times the upper limit of the normal range.[13] In one study of 35 infants born to mothers with GD, an increased maternal TRAb level 5 times greater than the normal range predicted neonatal thyrotoxicosis with a sensitivity of 100% and specificity of 76%.[15] In cases of poorly controlled maternal GD, maternal thyrotoxicosis can also cause central hypothyroidism, presumably through suppression of development of the fetal hypothalamic-pituitary-thyroid axis (see **Fig. 1**).[16] If maternal TRAb is negative during screening between 20 and 24 gestational weeks, and the mother is not on any ATD, then the baby is not at risk for development of neonatal GD and does not require any specific screening.

Early diagnosis of fetal hyperthyroidism can help prevent complications. Serial fetal ultrasonography, especially in cases of fetuses determined to be at increased risk based on high maternal TRAb level, should be performed by an experienced fetal ultrasonographer.[17,18] Nomograms for fetal thyroid gland surveillance have been

developed.[19] Fetal ultrasonography should be completed at 20 weeks' gestation and then repeated every 4 to 6 weeks, particularly in cases of poorly controlled maternal hyperthyroidism.[10] It is important to distinguish fetal goiters caused by fetal hyperthyroidism from those caused by fetal hypothyroidism that may result from transplacental passage of maternal ATD. Examination of the vascularity of the goiter, as well as assessments of bone maturation and fetal heart rate, may guide determination of whether fetal hyperthyroidism or hypothyroidism is present.[10] Increased blood flow on Doppler ultrasonography imaging at the periphery of the thyroid is associated with hypothyroidism-induced goiter, and increased blood flow throughout the fetal goiter is associated with hyperthyroidism-induced fetal goiter.[17]

Management During Pregnancy

Pregnant women with hyperthyroidism/GD should be treated with medical therapy. Fetal hyperthyroidism can generally be prevented by adequate administration of ATDs to the mother. ATDs used for treatment of maternal GD include propylthiouracil (PTU) and methimazole (MMI), the active metabolite of carbimazole. The goal of therapy is to keep maternal free T4 (fT4) levels in the upper half of the normal range to maintain euthyroidism in the fetus.[13] Pregnant women with active GD should be treated with PTU rather than MMI during the first trimester, because of the increased risk for congenital anomalies associated with MMI.[12,13] A recent meta-analysis of 12 studies involving exposure to different ATDs during pregnancy found that exposure to MMI compared with PTU significantly increased the risk of neonatal congenital malformations.[20] Risks associated with MMI use include choanal or esophageal atresia, omphalomesenteric duct abnormalities, aplasia cutis, and dysmorphic facies. During the second and third trimesters, after the period linked with increased risk for congenital anomalies has passed, it is recommended that the ATD be switched from PTU to MMI because of increased risk for PTU-associated hepatotoxicity in the mother.[12]

RAI should not be administered to women attempting to conceive within 6 months of RAI treatment because of the increased risk of inducing neonatal or fetal hyperthyroidism secondary to RAI-increased maternal titers of TRAb or the risk of causing fetal hypothyroidism secondary to transplacental transport of the RAI. Surgical treatment would be favored as the definitive treatment before pregnancy but should only be considered during pregnancy if the mother has had a severe adverse reaction to ATD therapy or if very high doses of ATD are necessary (>30 mg/d of MMI or >450 mg/d of PTU), either secondary to refractory disease or to poor compliance. If surgery is required, the optimal timing is during the second trimester.[12,13]

Fetal hyperthyroidism can be managed by treatment of the mother with ATDs. In cases of maternal GD with TRAb positivity and suspected fetal hyperthyroidism, the maternal ATD dose may need to be increased to reduce fetal signs of hyperthyroidism. Normalization of fetal heart rate is a goal of maternal therapy. In contrast, if fetal hypothyroidism is suspected, the maternal ATD dose may need to be decreased.[10]

NEONATAL HYPERTHYROIDISM: NEONATAL ASPECTS

Manifestations of Hyperthyroidism in Neonates

Following birth, newborns may present with tachycardia, irritability with tremors, poor feeding, sweating, and difficulty sleeping secondary to thyrotoxicosis (see **Box 1**). Newborns may also have an emaciated appearance, proptosis with stare, and a goiter. Premature closure of cranial sutures (craniosynostosis) and subsequent microcephaly may be noted in severely affected infants. Other rare signs of neonatal hyperthyroidism that may be confused with infection/sepsis include thrombocytopenia,

hepatosplenomegaly, and jaundice.[21] There have been reports of fulminant liver failure and pulmonary hypertension secondary to neonatal hyperthyroidism caused by maternal GD.[22–25]

In addition to having significant morbidity, neonates with hyperthyroidism are at increased risk for mortality without prompt treatment. In older case series, mortalities up to 12% to 20% have been reported, with cardiac failure the most common cause of death.[4]

Screening for Neonatal Hyperthyroidism

A screening algorithm for newborns at risk for neonatal thyrotoxicosis has been adapted from a recent review and is shown in **Fig. 2**.[26] Neonates considered to be at high risk for development of thyrotoxicosis include (1) infants born to mothers with GD, especially if the maternal TRAb level is great than 2 to 3 times the upper limit of normal; (2) infants in whom intrauterine surveillance revealed fetal signs of hyperthyroidism; and (3) infants with a known family history of genetic causes of congenital hyperthyroidism, including activating mutations in the TSHR (**Box 2**).

The algorithm in **Fig. 2** outlines recommended laboratory and clinical assessment for the first 2 weeks of life. If possible, TRAb levels should be determined in cord blood of infants at high risk for neonatal hyperthyroidism. Studies have shown strong correlations between maternal and neonatal TRAb levels. In one cohort study, 73% of newborns born to mothers with positive TRAb had increased cord blood TRAb levels, and 29% of these newborns subsequently developed neonatal hyperthyroidism.[27] Increased fT4 level between 3 and 7 days of life, but not at birth, was predictive of the development of hyperthyroidism in this study. Other studies have also shown that cord blood thyroid-stimulating hormone (TSH) and fT4 are less valuable in predicting onset of neonatal hyperthyroidism. Overall, the utility of cord blood TSH and fT4 levels in predicting onset of neonatal hyperthyroidism has not been established, and it is not recommended to obtain TSH and free T4 levels with cord blood.[26]

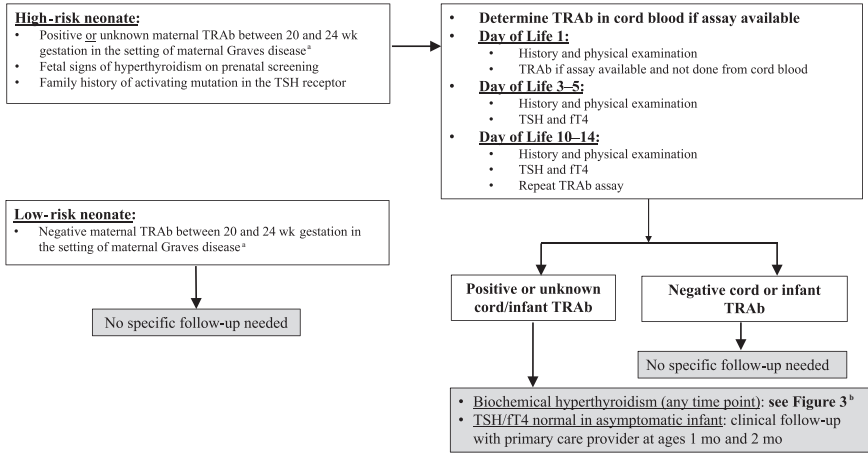

Fig. 2. Screening algorithm for newborns at risk for neonatal thyrotoxicosis. [a]Maternal TRAb level should be obtained in pregnant women with active or past GD/hyperthyroidism. [b]Neonates born to mothers with GD are also at risk for primary or central hypothyroidism and, in those cases, may require thyroid hormone replacement with levothyroxine. (*Adapted from* van der Kaay DC, Wasserman JD, Palmert MR. Management of neonates born to mothers with Graves' disease. Pediatrics 2016;137:e20151878.)

Box 2
Neonates at increased risk for thyrotoxicosis

Mother

- Increased TRAb/TSI levels during pregnancy
  - Active GD (hyperthyroidism)
  - Following treatment of GD with RAI
  - Following surgical treatment of GD (thyroidectomy)
- TRAb/TSI levels not assessed during pregnancy (unknown)
- ATD use during second/third trimester
- Clinical thyrotoxicosis during the second/third trimester
- Prior child with neonatal GD
- Family history of TSHR mutation

Baby

- Evidence of fetal thyrotoxicosis

Adapted from Ogilvy-Stuart AL. Neonatal thyroid disorders. Arch Dis Child Fetal Neonatal Ed 2002;87(3):F165–71.

If the neonate's TRAb level has not been obtained from cord blood, it should be determined as soon as possible after birth. Depending on how quickly TRAb results return from a particular laboratory, this level may not be available to inform clinical decision making. The newborn should be monitored closely for clinical and biochemical signs of overt hyperthyroidism. Maternal ATDs are usually metabolized and excreted by 5 days of life. Unless symptoms of hyperthyroidism develop earlier, thyroid function studies (TSH and fT4) should be sent between 3 and 5 days of life, when biochemical hyperthyroidism typically develops in neonates with hyperthyroidism secondary to maternal GD. Onset of signs and symptoms of thyrotoxicosis may be delayed for several days, either from the effect of maternal ATDs or because of the coexistent effect of blocking antibodies. Thyroid function studies should therefore be sent again at 10 to 14 days of life, because studies have shown that most cases of neonatal GD present within the first 2 weeks of life.[26] However, there have been case reports of overt thyrotoxicosis secondary to neonatal GD occurring as late as 45 days of life.[4] After 2 weeks of age, infants with no clinical or biochemical hyperthyroidism should continue close monthly follow-up with their primary care providers. Anticipatory guidance regarding signs of hyperthyroidism should be provided for parents.

Management of Neonatal Hyperthyroidism

A treatment algorithm for neonatal thyrotoxicosis has been adapted from a recent review (2016) and is shown in **Fig. 3**.[26] In cases of suspected neonatal GD with biochemical hyperthyroidism, MMI should be started at a dose of 0.2 to 0.5 mg/kg/d. Propranolol should be added at a dose of 2 mg/kg/d for signs of sympathetic hyperactivity, including tachycardia and hypertension. PTU is not recommended in neonates and throughout childhood because of the increased risk for hepatotoxicity.[28] In severe cases with hemodynamic compromise, Lugol solution or potassium iodide may be given. Glucocorticoids may also be beneficial in the short term. Because neonatal hyperthyroidism is transient and resolves with clearance of maternal TRAb from the circulation, thyroid function tests should be monitored closely every 1 to 2 weeks following initiation of treatment to ensure appropriate MMI dose titration.[26]

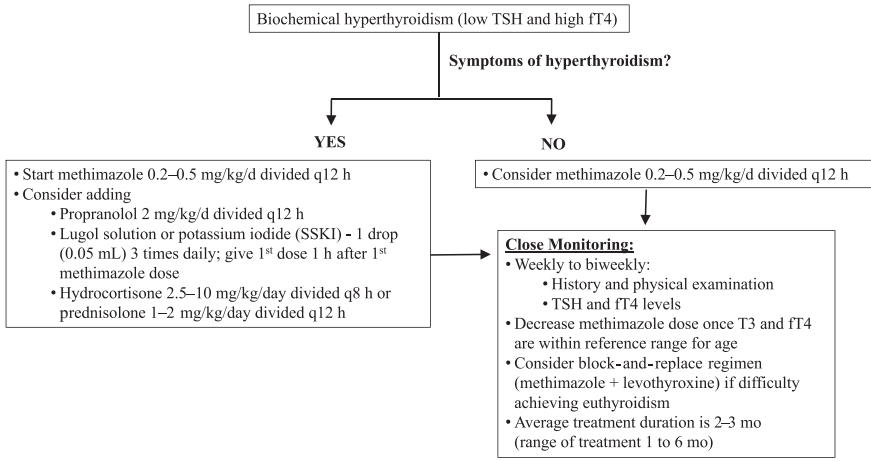

Fig. 3. Management for neonates with thyrotoxicosis. q, every; T3, triiodothyronine. (*Adapted from* van der Kaay DC, Wasserman JD, Palmert MR. Management of neonates born to mothers with Graves' disease. Pediatrics 2016;137:e20151878.)

The benefit of treatment of asymptomatic biochemical hyperthyroidism has not been shown as clearly.[26]

In cases of nonautoimmune neonatal hyperthyroidism (activating mutations of the TSHR or McCune-Albright syndrome), MMI should be used for treatment similarly to cases of neonatal GD. Definitive therapy, including thyroidectomy and/or RAI will ultimately be required but can be delayed for months to years if the baby is responsive to medical therapy.[29,30]

Current guidelines note that breastfeeding is safe for mothers on antithyroid medications, at moderate doses of MMI (20–30 mg/d) and PTU (<300 mg/d).[31] Infants of mothers with GD who are breastfeeding should have periodic thyroid function screening to ensure they have not developed hypothyroidism. In one study of 42 breastfeeding mothers with hyperthyroidism treated with moderate doses of MMI, no significant differences in growth or intellectual development were seen in children at follow-up at age 48 to 84 months.[32]

OUTCOMES OF NEONATAL THYROTOXICOSIS

In addition to the well-documented short-term consequences, there is some evidence to suggest that there are long-term negative outcomes of neonatal thyrotoxicosis, particularly if inadequately treated. Normal thyroid hormone levels are important for normal brain development, and the adverse neurocognitive effects of congenital hypothyroidism are well known. In contrast, studies of neurocognitive outcomes of infants with thyrotoxicosis are limited. One study of 8 children with histories of neonatal thyrotoxicosis showed intellectual impairment and craniosynostosis in 6 children and intellectual impairment in 4 children at age 2 years or older.[33] Another study of 17 children of hyperthyroid mothers receiving ATDs during pregnancy showed no effects of ATD treatment on thyroid gland size/function or physical and intellectual development after the neonatal period.[34] Further studies are needed to assess whether neonatal hyperthyroidism leads to long-term complications. Results will help inform management strategies in order to optimize patient outcomes.

SUMMARY

Infants at risk for development of neonatal hyperthyroidism benefit from a multidisciplinary approach to care beginning prenatally, including a team of obstetricians and radiologists with expertise in maternal-fetal medicine, neonatologists, pediatricians, and pediatric endocrinologists. Quality improvement initiatives should be designed to ensure proper implementation of screening guidelines for pregnant women with hyperthyroidism as well as appropriate screening and management for fetal/neonatal hyperthyroidism. Early diagnosis and commencement of therapy is necessary to prevent short-term and potential long-term adverse outcomes of neonatal thyrotoxicosis. Future studies are needed to assess the long-term effects of neonatal thyrotoxicosis, including impacts on thyroid function, growth, and cognitive development.

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