Neonatal Thyrotoxicosis

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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**).

Disclosure: The authors do not have any commercial or financial conflicts of interested to report.
Funding: Research reported in this article for (S.L. Samuels) was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number TL1TR001880. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
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Clin Perinatol ■ (2017) ■–■
https://doi.org/10.1016/j.clp.2017.10.001
perinatology.theclinics.com

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