Management of Neonates Born to Mothers With Graves' Disease

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abstract

Neonates born to mothers with Graves' disease are at risk for significant morbidity and mortality and need to be appropriately identified and managed. Because no consensus guidelines regarding the treatment of these newborns exist, we sought to generate a literature-based management algorithm. The suggestions include the following: (1) Base initial risk assessment on maternal thyroid stimulating hormone (TSH) receptor antibodies. If levels are negative, no specific neonatal follow-up is necessary; if unavailable or positive, regard the newborn as "at risk" for the development of hyperthyroidism. (2) Determine levels of TSH-receptor antibodies in cord blood, or as soon as possible thereafter, so that newborns with negative antibodies can be discharged from follow-up. (3) Measurement of cord TSH and fT4 levels is not indicated. (4) Perform fT4 and TSH levels at day 3 to 5 of life, repeat at day 10 to 14 of life and follow clinically until 2 to 3 months of life. (5) Use the same testing schedule in neonates born to mothers with treated or untreated Graves' disease. (6) When warranted, use methimazole (MMI) as the treatment of choice; β-blockers can be added for sympathetic hyperactivity. In refractory cases, potassium iodide may be used in conjunction with MMI. The need for treatment of asymptomatic infants with biochemical hyperthyroidism is uncertain. (7) Assess the MMI-treated newborn on a weekly basis until stable, then every 1 to 2 weeks, with a decrease of MMI (and other medications) as tolerated. MMI treatment duration is most commonly 1 to 2 months. (8) Be cognizant that central or primary hypothyroidism can occur in these newborns.

Over the course of their careers, many family doctors, pediatricians, and neonatologists will manage the offspring of a mother with Graves' disease (GD). Such newborns are at risk for developing neonatal hyperthyroidism with its potential morbidity and mortality and require close monitoring after birth. Despite its importance, there are no consensus guidelines for the management of these newborns. We therefore conducted a literature review to develop an approach to guide clinicians caring for these newborns.

BACKGROUND

The prevalence of maternal hyperthyroidism due to GD in pregnancy varies from 0.1% to 2.7%.[1–4] The prevalence of transient GD in infants born to these mothers is uncertain, varying from 1.5% to 2.5%[5–7] up to 20.0% in observational cohort studies.[7–9]

The causative antibodies in GD, thyroid-stimulating hormone (TSH) receptor antibodies (TRAb), belong to the immunoglobulin G class and freely cross the placenta, particularly during the second half of pregnancy.[10] There are 2 types of TRAb. TSH-receptor

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stimulating antibodies bind to the TSH-receptor on thyroid follicular cells and lead to autonomous thyroid hormone production. TSH-receptor blocking antibodies bind to the TSH-receptor but do not initiate intracellular signaling. Because fetal thyroid development is established by 7 weeks' gestation, thyroid hormone synthesis begins at 10 to 12 weeks of gestation, and the thyroid is largely functionally mature by 25 weeks of gestation, transfer of stimulating TRAb to the fetus can cause in utero and/or postnatal hyperthyroidism.[11]

When present, fetal hyperthyroidism is most commonly seen during the third trimester. Signs of fetal GD include tachycardia, heart failure with non-immune hydrops, intrauterine growth retardation, preterm birth, advanced skeletal maturation, and craniosynostosis. In symptomatic cases, fetal hyperthyroidism may be treated by administering antithyroid drugs (ATDs) to the mother.[12,13]

Neonatal signs and symptoms of GD are multifaceted. Findings include goiter with occasional tracheal compression, low birth weight, stare, periorbital edema, retraction of the eyelid, hyperthermia, irritability, diarrhea, feeding difficulties, poor weight gain, tachycardia, heart failure, hypertension, hepatomegaly, splenomegaly, cholestasis, thrombocytopenia, and hyperviscosity.[6,11,14–17] Signs and symptoms of neonatal hyperthyroidism are nonspecific and also could be attributed to congenital viral infections or sepsis.[18] The diagnosis of neonatal hyperthyroidism can therefore be overlooked, resulting in preventable morbidity and mortality, with mortality rates up to 20% reported.[6] Neonatal complication rates are higher in women who remain hyperthyroid during the second half of pregnancy.[19]

Worries about clinical instability are a salient reason to treat a newborn with GD. Although controversial, some authors believe initiating treatment positively affects neurocognitive outcomes. Normal thyroid hormone levels are essential for normal brain development, but data regarding neurodevelopmental outcomes in children born to mothers with GD during pregnancy are scarce. No differences in total IQ and verbal and performance skills were found in 31 patients aged 4 to 23 years (median age 11 years) born to mothers with GD, compared with 25 controls; all patients were euthyroid at birth.[20] Similar results were found in 2 other studies.[21,22] In contrast, in 8 children with neonatal hyperthyroidism, craniosynostosis was identified in 6 and intelligence tests were below average in 4 at ages 2 years or older.[23] Growth in children born to mothers with GD during pregnancy is comparable to unaffected controls.[22,23]

Key issues in the management of newborns of mothers with GD include the timing of first determination of free T4 (fT4) and TSH levels (thyroid function tests [TFTs]), the frequency and duration of follow-up, and indications for treatment. To inform these decisions, we sought to develop a management algorithm (Fig 1) that addresses the following questions:

- Is there an association between maternal TRAb levels and risk of neonatal hyperthyroidism?
- Is there utility to determination of TRAb levels in cord blood?
- Are cord blood TSH and fT4 levels valuable in predicting neonatal hyperthyroidism?
- When should TSH and fT4 levels be measured in the "at-risk" newborn?
- Do maternal ATDs influence the newborn's presentation?
- What clinical indicators should prompt initiation of treatment?

- How long should ATD treatment be continued?
- Are there other abnormalities of thyroid function in newborns born to mothers with GD?

METHODS

Medline, Embase, and Cochrane databases were searched with the assistance of a reference librarian from our hospital. The following Medline MeSH terms were used: "Graves disease," "hyperthyroidism," or "thyrotoxicosis." Search limits included publication in the past 15 years (January 1, 2000–May 22, 2015); English language, and infants (0–23 months). This search resulted in 283 publications. After reviewing the abstracts, 179 articles were not applicable. The remaining 104 articles were read and 68 were included in this review; the other 36 articles addressed topics beyond the scope of this review. In addition, we included 18 pre-2000 original reports cited as references in the 68 articles. The literature includes case reports, case series, and observational cohort studies; we did not identify relevant randomized controlled studies or case-control studies. Thus, the quality of evidence was graded as moderate (observational studies with methodological flaws, inconsistent or indirect evidence) to low (case series and nonsystematic clinical observations). The strength of recommendation is weak (benefits and risks or burdens are closely balanced or uncertain, best action may differ depending on circumstances or patients).[24] We therefore used the term "suggestion" instead of "recommendation."

In this review, we denote "positive" TRAb levels as levels that exceeded the reference range. "Negative" TRAb levels denote levels within the reference range or that are undetectable. Because methimazole (MMI) is the active metabolite of carbimazole, we chose MMI and
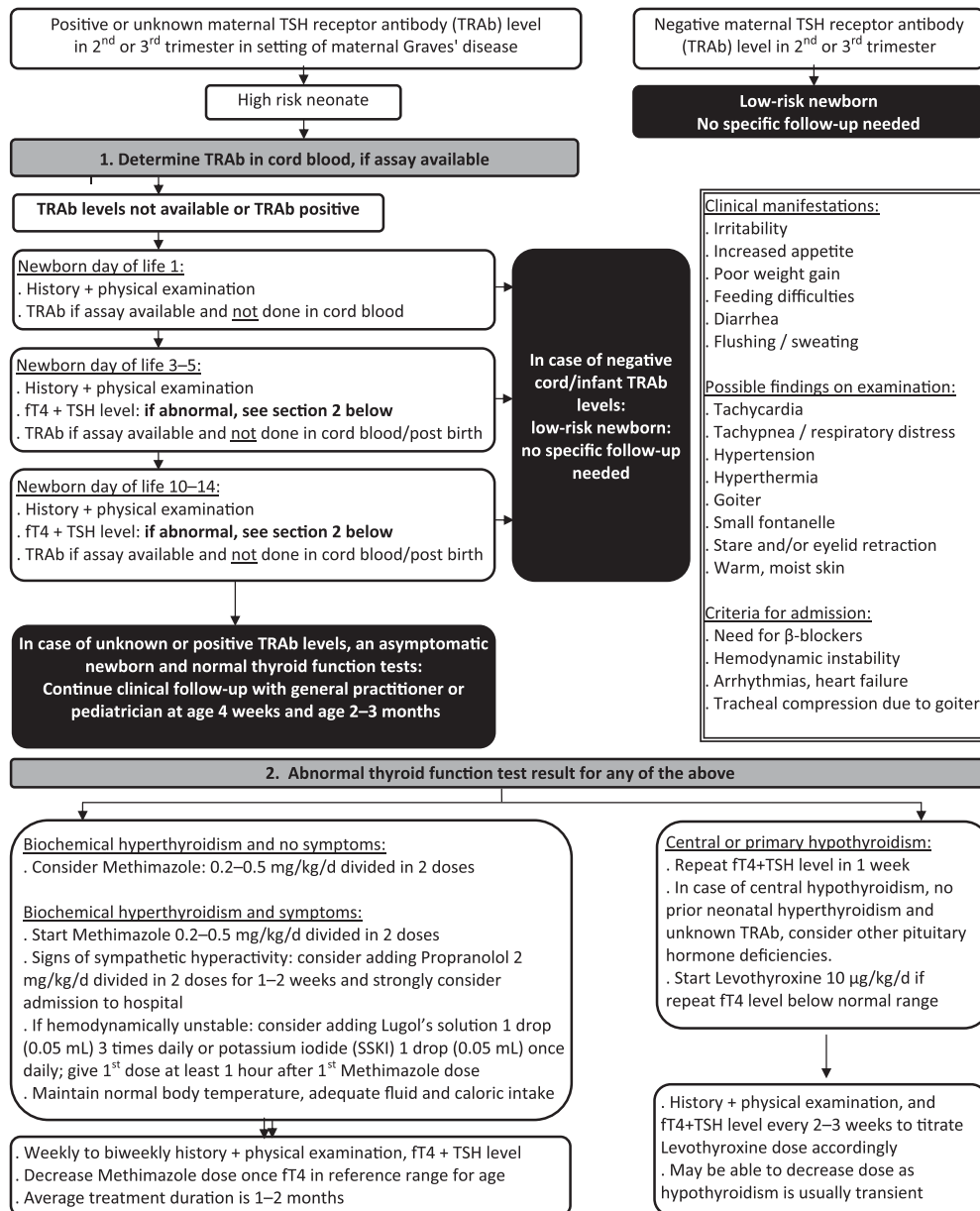
FIGURE 1
Management algorithm.

propylthiouracil (PTU) as the ATDs in this review.

DISCUSSION

Question 1: Is There an Association Between Maternal TRAb Levels and Risk of Neonatal Hyperthyroidism?

TRAb levels are present in mothers with active GD; however, they can also persist after definitive therapy. After subtotal thyroidectomy

and ATD treatment, TRAb levels continued to be elevated in 20% to 30% of patients on average 1.5 years after treatment. Five years after radioactive iodine treatment, TRAb levels continued to be elevated in 40% of patients.[25]

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

in women with active or past GD or a previous infant with neonatal GD.[5,26]

Strong correlations between maternal and neonatal TRAb levels have been documented.[9,27,28] Elevated cord TRAb levels were found in 73% of newborns born to mothers with elevated TRAb levels in the third trimester.[9] Furthermore, elevated maternal TRAb levels are associated with an increased risk of overt neonatal

hyperthyroidism.[7–9,27–33] In a study that included 35 pregnancies in 29 women with GD, 6 newborns (17.1%) developed hyperthyroidism. TRAb levels fourfold above the reference range predicted neonatal hyperthyroidism with a positive predictive value of 40%, whereas levels less than fourfold above the reference range were associated with a negative predictive value of 100%.[8] In another study describing 230 pregnancies in 172 women with GD, 6 newborns (2.6%) developed overt hyperthyroidism and another 7 (3.0%) developed asymptomatic biochemical hyperthyroidism. Maternal TRAb levels were twofold to fivefold above the reference range in 8 of these 13 newborns.[7] In a recent report, none of 35 infants born to mothers with negative TRAb levels during pregnancy developed hyperthyroidism.[9] The risk of neonatal hyperthyroidism after being born to women with negative TRAb levels is therefore regarded as negligible.[34]

There are currently 2 methods to measure TRAb levels. Second-generation receptor binding assays measuring thyroid-binding inhibitory immunoglobulins are widely available, but do not distinguish between stimulating and nonstimulating immunoglobulins. Third-generation bioassays measure thyroid-stimulating or blocking immunoglobulins through cyclic adenosine monophosphate production.[35] These bioassays are less widely available, time-consuming, and more expensive. It has been demonstrated that a maternal thyroid-binding inhibitory immunoglobulin level of >3.3 times the upper reference range had a sensitivity of 100% and specificity of 43% for identifying affected newborns. Thyroid-stimulating antibody activity exceeding 400% (considered "strong" activity) increased the specificity to 85%[35]; however, generalizing exact numeric

cutoffs is confounded by lack of assay harmonization. Laboratories involved in the care of these newborns should state clearly which assay is used.[36,37]

Suggestion:

TRAb levels should be determined between weeks 20 and 24 of pregnancy. If maternal TRAb levels are negative, no specific GD-related follow-up is necessary. If TRAb levels are unavailable or positive, the newborn should be regarded as being "at risk" for hyperthyroidism.

Question 2: Is Determination of TRAb Levels in Cord Blood Useful?

Skuza et al[38] compared TRAb levels in 14 infants born to mothers with GD. Cord blood TRAb levels were normal in 7 infants who remained euthyroid, whereas levels were threefold to sixfold above the reference range in 7 infants who developed hyperthyroidism. Similarly, Besançon et al[9] described 9 of 9 newborns with negative cord blood TRAb levels who remained euthyroid. Several other studies also have demonstrated that positive TRAb levels in cord blood correlate with the likelihood of development of hyperthyroidism in the first 2 weeks of life, whereas negative antibodies are associated with little or no risk of neonatal hyperthyroidism.[9,30,38,39] Positive cord TRAb levels (up to 2.5 times the assay upper reference limit), however, have been reported in newborns with normal thyroid function,[40] demonstrating that low levels of antibodies can be seen in euthyroid newborns.

Although TRAb levels provide important clinical information, the utility of cord blood TRAb levels can be limited by the availability of the test and the turnaround time, which varies between 1 day and 2 weeks.

Suggestion:

If the assay is available, determine TRAb levels in cord blood, or as soon as possible thereafter, as this will

allow those newborns with negative antibodies to be discharged from follow-up.

Question 3: Are Cord Blood TSH and fT4 Levels Valuable in Predicting Neonatal Hyperthyroidism?

Several studies have demonstrated that cord blood TSH and fT4 levels reflect fetal thyroid function but do not predict neonatal thyroid function.[30,38,39] Among 6 newborns who developed hyperthyroidism, Polak et al[40] demonstrated that cord blood levels indicated hyperthyroidism, hypothyroidism, and euthyroidism in equal numbers. A recent observational study included 68 women with GD; all women were receiving ATD treatment and were well-controlled. Of 7 newborns who developed hyperthyroidism, 2 had hypothyroidism in cord blood tests.[9] Collectively these studies demonstrate that cord blood TSH and fT4 levels do not reliably predict the risk of neonatal hyperthyroidism.

Suggestion:

Determination of cord TSH and fT4 levels is not indicated, because these levels do not predict neonatal hyperthyroidism.

Question 4: When Should TSH and fT4 Levels Be Measured in the "At-Risk" Newborn?

Overt neonatal hyperthyroidism can present at birth; however, the onset can be delayed due to maternal ATD treatment (as discussed in question 5) or the coexistence of TSH-receptor blocking antibodies. Several reports demonstrate that >95% of newborns who develop symptoms, do so between 1 and 29 days of life and most are diagnosed within the first 2 weeks.[9,38,40,41]

In 1 study, fT4 and TSH levels were determined in 96 at-risk newborns during the first month of life.[42] Four (4%) newborns developed clinical hyperthyroidism, the ages of onset were not specified. In the full group,

fT4 levels peaked and were above the 95th percentile in 92.9% of newborns on day 5 of life, returning to the reference range at day 15. More than 60% of this cohort had a TSH level below the fifth percentile at day 6 of life. This study indicates that a significant proportion of at-risk newborns have abnormal TFTs without symptoms. Similar to cord blood, TFTs before 3 days of life did not predict subsequent hyperthyroidism; hence, these authors suggested first assessing TFTs at day 3 to 5 of life. Because TFTs normalized by day of life 15 in most asymptomatic newborns, the authors also suggested that, when thyroid function is normal at 2 weeks of life, no further testing is necessary. However, infants should continue to be followed clinically, because development of hyperthyroidism as late as day 45 of life has been described.[41–44]

These recommendations for the first 2 weeks of life are consistent with those of others.[6,9,40] After 2 weeks of life, Besançon et al[9] recommend weekly clinical and biochemical evaluation for all newborns with positive TRAb levels until levels become negative, although it is not clear if data support this level of prolonged and intensive monitoring in all infants.

The same temporal patterns appear to be present in preterm infants. One study described 7 preterm infants from 5 pregnancies born after a mean gestational age (GA) of 30 (range 25–36) weeks.[45] Mean age at diagnosis of hyperthyroidism was 9 (range 1–16) days. One infant developed thyroid storm characterized by tachypnea, tachycardia, cardiac failure, and pulmonary edema.

Whether asymptomatic newborns with biochemical hyperthyroidism should be treated is perhaps the greatest area of uncertainty in this population. Further data on neurocognitive outcomes (as

discussed in question 6) are needed to inform this decision. In the absence of definitive data, it seems prudent to obtain TFTs even among asymptomatic infants, as the results may inform clinical follow-up.

Suggestion:

TFTs should initially be measured at 3 to 5 days of life unless clinical signs warrant earlier investigations. If these data are within age-specific reference ranges, repeat TFTs at day 10 to 14 of life. If no abnormalities are identified after 2 weeks of life, routine testing can be discontinued. At 4 weeks of life and again at 2 and 3 months of life, infants should be assessed clinically to identify the small population of infants with delayed presentation. Because TSH and fT4 levels are influenced by variations in analytical assays, hospitals should establish age-specific reference ranges to inform these decisions.

Question 5: Do Maternal ATDs Influence the Newborn's Presentation?

ATDs can delay presentation of hyperthyroidism because these cross the placenta.[46] The duration of action of MMI is 36 to 72 hours and of PTU is 12 to 24 hours.[47] It has been reported that newborns born to untreated mothers tended to be diagnosed at day 1 to 3 of life, whereas newborns from mothers treated with ATDs were diagnosed between days 7 and 17.[41] These variations would be detected by using the schedule delineated previously and in Figure 1.

ATDs can reach the newborn through breast milk, but only in small quantities.[48] PTU in doses <300 mg per day and MMI <20 to 30 mg per day do not impair thyroid function in the newborn and are regarded as safe during breastfeeding.[26,49–51] Although there is insufficient literature to make a definitive statement, it seems unlikely that this degree of

medication transfer would affect the presentation of neonatal GD.

As this review focuses on evaluation and treatment of newborns, it is worth noting that MMI use during pregnancy has been associated with congenital anomalies in some[52–54] but not all[1,55,56] studies, and that high-dose PTU treatment has been associated with an increased risk of low birth weight.[3] Because PTU has (rarely) been associated with liver failure in pregnant women,[5,57] current guidelines recommend switching to MMI after the first trimester.[5,26]

Suggestion:

Although ATDs may delay the presentation of hyperthyroidism, the first TFTs should still be performed on day of life 3 to 5 in neonates born to mothers on ATD treatment, with subsequent testing as suggested previously.

Question 6: What Clinical Indications Should Prompt Initiation of Treatment?

Treatment should be initiated at the onset of symptoms to avoid short-term (cardiac failure) and long-term (craniosynostosis, intellectual impairment) complications. It is unclear whether asymptomatic newborns with biochemical hyperthyroidism should be treated, and it is difficult to compare thresholds used to initiate treatment in one study versus another, as different assays and different reference ranges confound direct comparison.

Among 7 newborns with clinical hyperthyroidism, PTU was initiated at an fT4 level >64 pmol/L (reference range 10–30 pmol/L) in 1 report.[38] In 6 patients who were asymptomatic, MMI was initiated at an average fT4 level of 49.6 pmol/L[40] in another report. Besançon et al,[9] who reported mostly on the same cohort as previously published by Polak et al[40] and Luton et al,[30]

describe ATD treatment being started between age 2 and 15 days when fT4 levels exceeded 35 pmol/L in 7 asymptomatic newborns (mean fT4 46.5 ± 13.8 pmol/L; reference range 21.5–27.8 pmol/L at day 7 and 16.9–20.2 pmol/L at day 15 of life).[9] The goal of the recommendation to start treatment when fT4 levels exceed 35 pmol/L is to prevent clinical hyperthyroidism with its potential morbidity and mortality.[9,40] However, data linking the initiation of therapy in these asymptomatic newborns with better clinical and neurocognitive outcomes are lacking. Related to this uncertainty, other case reports and series describe initiating treatment only when both biochemical hyperthyroidism, with fT4 levels ranging from 43 to 154 pmol/L, and symptoms were present.[14–18,42,58–66] Arguing against this approach is the small series reported by Daneman and Howard[23] in which untreated neonatal GD was associated with later-life cognitive impairment. Overall, the literature addressing treatment of asymptomatic newborns is inconclusive, as it comprises only a few studies, often with small numbers, and lacks defined outcomes and/or untreated control groups for comparison.

PTU and MMI inhibit thyroid peroxidase and consequently synthesis of thyroid hormone. PTU also inhibits peripheral deiodination of T4 to T3. In 2010, the US Food and Drug Administration issued a warning regarding the association between PTU and development of liver failure. Subsequent American Thyroid Association guidelines recommend that PTU should be offered only as a short course in case of thyroid storm or severe adverse reactions to MMI treatment, other than agranulocytosis, when treatment options such as radioactive iodine or thyroidectomy are not available.[67,68]

Because a response to ATDs is seen only once thyroid hormone stores are depleted, it can take several days to weeks before clinical and biochemical effects are noticeable. In symptomatic patients, nonselective β-adrenergic blockers such as propranolol can decrease sympathetic hyperactivity. In refractory cases, Lugol solution or potassium iodide (oral solution) can be added.[11] The first dose of iodide should be given at least 1 hour after the first dose of MMI to prevent the initial iodide from being used for new thyroid hormone synthesis. Less commonly, hyperthyroidism is (initially) treated with repeated doses of iodide instead of ATDs.[18,69–71] In extremely ill newborns requiring admission to a NICU for respiratory or cardiac support, a short course of glucocorticoids, which inhibit thyroid hormone secretion and impair peripheral deiodination of T4 to T3, may be necessary.

Side effects of MMI occur in up to 28% of children.[72] The most common side effects are mild, such as transient elevations of liver enzymes, mild and transient leukopenia, skin rashes, gastrointestinal symptoms, arthralgia, and myalgia.[68,72] Serious side effects (0.5% of children) include agranulocytosis, liver injury, vasculitis and Stevens-Johnson syndrome.[68,72] Agranulocytosis most commonly presents with fever, sore throat, or mouth sores. Parents should be instructed to stop ATDs immediately if these occur, consult a physician, and obtain a complete blood count. To the best of our knowledge, only a single case report described the development of neutropenia in a preterm (GA 30 weeks) neonate treated with MMI who recovered after decreasing the dose.[71]

Prematurity is not a contraindication to ATD use. However, in 1 study, 2 extremely preterm newborns (GA 25 weeks) demonstrated an unusually rapid (within 48 hours) decrease in

fT4 levels after starting carbimazole, indicating that is important to monitor TFTs more closely in preterm newborns.[45]

Suggestion:

Initiate treatment with MMI with signs or symptoms of neonatal hyperthyroidism in the setting of biochemical hyperthyroidism. Empiric therapy could be started after drawing TFTs in emergent situations. There is a lack of consensus regarding the starting dose for infants. A range from 0.2 to 1 mg/kg per day divided in 1 to 3 doses, with a typical dose of 0.2 to 0.5 mg/kg per day, has been reported.[14,59,64,66,71,73] For full-term newborns, we therefore recommend initiating MMI at 0.625 mg twice daily (0.4 mg/kg per day for a 3-kg newborn). The infant should be assessed clinically and biochemically on a weekly base until stable, then every 1 to 2 weeks with titration of MMI dose as tolerated. Treatment of asymptomatic neonates remains controversial.

With sympathetic hyperactivity, such as tachycardia, hypertension, and poor feeding, propranolol 2 mg/kg per day divided in 2 doses for 1 to 2 weeks can be added. Admission to hospital should be considered for cardiac monitoring and to ensure adequate fluid and caloric intake and temperature control. Lugol solution 1 drop (0.05 mL) 3 times per day or potassium iodide (oral solution) 1 drop per day may be used in conjunction with MMI. Hemodynamic instability, respiratory distress or cardiac failure warrants NICU admission. In these cases, a short course of treatment with prednisolone 2 mg/kg per day in 1 to 2 divided doses should be considered in addition to MMI.

Question 7: How Long Should ATD Treatment Be Continued?

Neonatal hyperthyroidism due to maternal GD is self-limited, with

duration determined by the rate of disappearance of maternal TRAb from the infant circulation. TRAb half-lives have been reported to be approximately 12 days.[74] Depending on the initial TRAb level, neonatal GD generally resolves by 6 months after birth,[35,38,41,75] although 1 instance of persistence to 12 months has been reported.[12] Treatment duration is most commonly 1 to 2 months.[6,9,35,38] MMI dose should be decreased and eventually discontinued when fT4 levels are within the reference range. Alternatively, the addition of levothyroxine to MMI treatment has been practiced,[9,14,59] although recent guidelines recommend against this "block and replace" practice.[73] The decision to discontinue treatment should be based on clinical status and ongoing normal thyroid hormone levels.

Suggestion:

While on treatment, thyroid function should be measured weekly until hormone levels are stable and subsequently every 2 weeks. Treatment duration is most commonly 1 to 2 months.

Question 8: Are There Other Abnormalities of Thyroid Function in Neonates Born to Mothers With GD?

In addition to neonatal hyperthyroidism, transient central hypothyroidism, transient primary hypothyroidism, and transient isolated hyperthyropinemia (elevated TSH with normal fT4 levels and no clinical symptoms) have been described.[9,39,76–83] One case series described 18 infants with central hypothyroidism born to mothers with GD who were inadequately treated during pregnancy. Eleven infants were diagnosed in the context of a primary T4-based newborn screening during days 4 and 7 of life. One infant presented with transient hyperthyroidism before evolving into central hypothyroidism. Six others were euthyroid before developing central

hypothyroidism during the first month of life. Seventeen infants started levothyroxine treatment.[76] Transient central hypothyroidism,[39,78,79] sometimes followed by hyperthyroidism,[80–82] has been reported by others. Recovery from hypothyroidism is usually seen between 3 and 19 months of age. Some physicians decrease levothyroxine supplementation as the hypothalamic-pituitary-thyroid axis recovers, but others advise ongoing treatment until 3 years of age to ensure adequate thyroid hormone levels during this important period of brain development.[76,83] In rare instances, central hypothyroidism can be prolonged and may be permanent.[83]

The etiology of central hypothyroidism in these infants is unknown but may stem from impaired maturation and/or regulation of the fetal hypothalamic-pituitary-thyroid axis. Another explanation invokes direct binding of TRAb to the TSH-receptor in the pituitary gland with suppression of TSH production independent of T4 production.[82,84]

Maternal ATD treatment has been associated with elevated cord blood TSH levels in 14% to 21% and low fT4 levels in 6% to 7% of newborns.[85] No relationship between TSH and fT4 levels with ATD dose was found. Other studies have found transiently elevated TSH levels and transient primary hypothyroidism in 7.8% and 2.0% to 9.0% of newborns, respectively.[7,33] Primary hypothyroidism can sometimes precede hyperthyroidism.[9] The interplay between TSH-receptor stimulating and blocking antibodies might explain the switch from hypothyroidism to hyperthyroidism and vice versa.[86,87]

Suggestion:

Be cognizant that central or primary hypothyroidism can occur in these

newborns. One must be aware of the clinical signs of hypothyroidism, including poor feeding, lethargy, prolonged jaundice, hypotonia, dry skin, large fontanelle, distended abdomen, umbilical hernia, and reduced linear growth, and monitor TFTs. Levothyroxine 10 μg/kg per day should be started when the diagnosis of hypothyroidism has been established. In the setting of central hypothyroidism without a previous diagnosis of hyperthyroidism, it is important to consider a differential diagnosis including pituitary dysfunction.

CONCLUSIONS

Neonatal hyperthyroidism due to maternal GD requires early recognition and treatment to prevent potential morbidity or mortality. We hope our literature review and related algorithm will assist generalists and subspecialists manage these patients. Refinement of this algorithm based on future studies and feedback on its use will be important.

ABBREVIATIONS

ATD: antithyroid drug
fT4: free T4
GA: gestational age
GD: Graves' disease
MMI: methimazole
PTU: propylthiouracil
TFT: thyroid function test
TRAb: TSH-receptor antibodies
TSH: thyroid stimulating hormone

REFERENCES

1. Korelitz JJ, McNally DL, Masters MN, Li SX, Xu Y, Rivkees SA. Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. *Thyroid*. 2013;23(6):758–765

2. Rivkees SA, Mandel SJ. Thyroid disease in pregnancy. *Horm Res Paediatr*. 2011;76(suppl 1):91–96

3. Chen CH, Xirasagar S, Lin CC, Wang LH, Kou YR, Lin HC. Risk of adverse perinatal outcomes with antithyroid treatment during pregnancy: a nationwide population-based study. *BJOG*. 2011;118(11):1365–1373

4. Wang W, Teng W, Shan Z, et al. The prevalence of thyroid disorders during early pregnancy in China: the benefits of universal screening in the first trimester of pregnancy. *Eur J Endocrinol*. 2011;164(2):263–268

5. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(8):2543–2565

6. Ogilvy-Stuart AL. Neonatal thyroid disorders. *Arch Dis Child Fetal Neonatal Ed*. 2002;87(3):F165–F171

7. Mitsuda N, Tamaki H, Amino N, Hosono T, Miyai K, Tanizawa O. Risk factors for developmental disorders in infants born to women with Graves disease. *Obstet Gynecol*. 1992;80(3 pt 1):359–364

8. Peleg D, Cada S, Peleg A, Ben-Ami M. The relationship between maternal serum thyroid-stimulating immunoglobulin and fetal and neonatal thyrotoxicosis. *Obstet Gynecol*. 2002;99(6):1040–1043

9. Besançon A, Beltrand J, Le Gac I, Luton D, Polak M. Management of neonates born to women with Graves' disease: a cohort study. *Eur J Endocrinol*. 2014;170(6):855–862

10. Pitcher-Wilmott RW, Hindocha P, Wood CB. The placental transfer of IgG subclasses in human pregnancy. *Clin Exp Immunol*. 1980;41(2):303–308

11. Polak M, Legac I, Vuillard E, Guibourdenche J, Castanet M, Luton D. Congenital hyperthyroidism: the fetus as a patient. *Horm Res*. 2006;65(5):235–242

12. Zimmerman D. Fetal and neonatal hyperthyroidism. *Thyroid*. 1999;9(7):727–733

13. Polak M, Van Vliet G. Therapeutic approach of fetal thyroid disorders. *Horm Res Paediatr*. 2010;74(1):1–5

14. Regelmann MO, Sullivan CK, Rapaport R. Thyroid "vise" in an infant with neonatal Graves' disease. *Pediatrics*. 2013;132(4). Available at: www.pediatrics.org/cgi/content/full/132/4/e1048

15. Loomba-Albrecht LA, Bremer AA, Wong A, Philipps AF. Neonatal cholestasis caused by hyperthyroidism. *J Pediatr Gastroenterol Nutr*. 2012;54(3):433–434

16. Oden J, Cheifetz IM. Neonatal thyrotoxicosis and persistent pulmonary hypertension necessitating extracorporeal life support. *Pediatrics*. 2005;115(1). Available at: www.pediatrics.org/cgi/content/full/115/1/e105

17. Obeid R, Kalra VK, Arora P, Quist F, Moltz KC, Chouthai NS. Neonatal thyrotoxicosis presenting as persistent pulmonary hypertension. *BMJ Case Rep*. 2012;2012

18. Carroll DN, Kamath P, Stewart L. Congenital viral infection? *Lancet*. 2005;365(9464):1110

19. Mestman JH. Hyperthyroidism in pregnancy. *Clin Obstet Gynecol*. 1997;40(1):45–64

20. Eisenstein Z, Weiss M, Katz Y, Bank H. Intellectual capacity of subjects exposed to methimazole or propylthiouracil in utero. *Eur J Pediatr*. 1992;151(8):558–559

21. Smit BJ, Kok JH, Vulsma T, Briët JM, Boer K, Wiersinga WM. Neurologic development of the newborn and young child in relation to maternal thyroid function. *Acta Paediatr*. 2000;89(3):291–295

22. Messer PM, Hauffa BP, Olbricht T, Benker G, Kotulla P, Reinwein D. Antithyroid drug treatment of Graves' disease in pregnancy: long-term effects on somatic growth, intellectual development and thyroid function of the offspring. *Acta Endocrinol (Copenh)*. 1990;123(3):311–316

23. Daneman D, Howard NJ. Neonatal thyrotoxicosis: intellectual impairment and craniosynostosis in later years. *J Pediatr*. 1980;97(2):257–259

24. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the effective health-care program. *J Clin Epidemiol*. 2010;63(5):513–523

25. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G,

Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *Eur J Endocrinol.* 2008;158(1):69–75

26. Stagnaro-Green A, Abalovich M, Alexander E, et al; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid.* 2011;21(10):1081–1125

27. Matsuura N, Konishi J, Fujieda K, et al. TSH-receptor antibodies in mothers with Graves' disease and outcome in their offspring. *Lancet.* 1988;1(8575-6): 14–17

28. Mortimer RH, Tyack SA, Galligan JP, Perry-Keene DA, Tan YM. Graves' disease in pregnancy: TSH receptor binding inhibiting immunoglobulins and maternal and neonatal thyroid function. *Clin Endocrinol (Oxf).* 1990;32(2):141–152

29. Hamada N, Momotani N, Ishikawa N, et al. Persistent high TRAb values during pregnancy predict increased risk of neonatal hyperthyroidism following radioiodine therapy for refractory hyperthyroidism. *Endocr J.* 2011;58(1):55–58

30. Luton D, Le Gac I, Vuillard E, et al. Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. *J Clin Endocrinol Metab.* 2005;90(11):6093–6098

31. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid.* 1992;2(2):155–159

32. Clavel S, Madec AM, Bornet H, Deviller P, Stefanutti A, Orgiazzi J. Anti TSH-receptor antibodies in pregnant patients with autoimmune thyroid disorder. *Br J Obstet Gynaecol.* 1990;97(11):1003–1008

33. Uenaka M, Tanimura K, Tairaku S, Morioka I, Ebina Y, Yamada H. Risk factors for neonatal thyroid dysfunction in pregnancies complicated by Graves' disease.

Eur J Obstet Gynecol Reprod Biol. 2014;177:89–93

34. Laurberg P, Nygaard B, Glinoer D, Grussendorf M, Orgiazzi J. Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidence-based symposium organized by the European Thyroid Association. *Eur J Endocrinol.* 1998;139(6):584–586

35. Abeillon-du Payrat J, Chikh K, Bossard N, et al. Predictive value of maternal second-generation thyroid-binding inhibitory immunoglobulin assay for neonatal autoimmune hyperthyroidism. *Eur J Endocrinol.* 2014;171(4):451–460

36. Barbesino G, Tomer Y. Clinical review: Clinical utility of TSH receptor antibodies. *J Clin Endocrinol Metab.* 2013;98(6):2247–2255

37. Tan K, Loh TP, Sethi S. Lack of standardized description of TRAb assays. *Endocrine.* 2013;43(3):732–733

38. Skuza KA, Sills IN, Stene M, Rapaport R. Prediction of neonatal hyperthyroidism in infants born to mothers with Graves disease. *J Pediatr.* 1996;128(2):264–268

39. Tamaki H, Amino N, Takeoka K, et al. Prediction of later development of thyrotoxicosis or central hypothyroidism from the cord serum thyroid-stimulating hormone level in neonates born to mothers with Graves disease. *J Pediatr.* 1989;115(2):318–321

40. Polak M, Le Gac I, Vuillard E, et al. Fetal and neonatal thyroid function in relation to maternal Graves' disease. *Best Pract Res Clin Endocrinol Metab.* 2004;18(2):289–302

41. Papendieck P, Chiesa A, Prieto L, Gruñeiro-Papendieck L. Thyroid disorders of neonates born to mothers with Graves' disease. *J Pediatr Endocrinol Metab.* 2009;22(6):547–553

42. Levy-Shraga Y, Tamir-Hostovsky L, Boyko V, Lerner-Geva L, Pinhas-Hamiel O. Follow-up of newborns of mothers with Graves' disease. *Thyroid.* 2014;24(6):1032–1039

43. Zakarija M, McKenzie JM, Hoffman WH. Prediction and therapy of intrauterine and late-onset neonatal hyperthyroidism. *J Clin Endocrinol Metab.* 1986;62(2):368–371

44. Uçkun Kitapçı A, Çalıkoğlu AS. Neonatal hyperthyroidism associated with isolated submandibular sialadenitis: is it just a coincidence? *J Clin Res Pediatr Endocrinol.* 2010;2(1):43–45

45. Smith C, Thomsett M, Choong C, Rodda C, McIntyre HD, Cotterill AM. Congenital thyrotoxicosis in premature infants. *Clin Endocrinol (Oxf).* 2001;54(3):371–376

46. Mortimer RH, Cannell GR, Addison RS, Johnson LP, Roberts MS, Bernus I. Methimazole and propylthiouracil equally cross the perfused human term placental lobule. *J Clin Endocrinol Metab.* 1997;82(9):3099–3102

47. Clark SM, Saade GR, Snodgrass WR, Hankins GD. Pharmacokinetics and pharmacotherapy of thionamides in pregnancy. *Ther Drug Monit.* 2006;28(4):477–483

48. Mandel SJ, Cooper DS. The use of antithyroid drugs in pregnancy and lactation. *J Clin Endocrinol Metab.* 2001;86(6):2354–2359

49. Momotani N, Yamashita R, Makino F, Noh JY, Ishikawa N, Ito K. Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol (Oxf).* 2000;53(2):177–181

50. Speller E, Brodribb W. Breastfeeding and thyroid disease: a literature review. *Breastfeed Rev.* 2012;20(2):41–47

51. Azizi F, Bahrainian M, Khamseh ME, Khoshniat M. Intellectual development and thyroid function in children who were breast-fed by thyrotoxic mothers taking methimazole. *J Pediatr Endocrinol Metab.* 2003;16(9):1239–1243

52. Clementi M, Di Gianantonio E, Cassina M, Leoncini E, Botto LD, Mastroiacovo P; SAFE-Med Study Group. Treatment of hyperthyroidism in pregnancy and birth defects. *J Clin Endocrinol Metab.* 2010;95(11):E337–E341

53. Yoshihara A, Noh J, Yamaguchi T, et al. Treatment of Graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *J Clin Endocrinol Metab.* 2012;97(7):2396–2403

54. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. *J Clin Endocrinol Metab*. 2013;98(11):4373–4381

55. Rosenfeld H, Ornoy A, Shechtman S, Diav-Citrin O. Pregnancy outcome, thyroid dysfunction and fetal goitre after in utero exposure to propylthiouracil: a controlled cohort study. *Br J Clin Pharmacol*. 2009;68(4):609–617

56. Di Gianantonio E, Schaefer C, Mastroiacovo PP, et al. Adverse effects of prenatal methimazole exposure. *Teratology*. 2001;64(5):262–266

57. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. *J Clin Endocrinol Metab*. 2009;94(6):1881–1882

58. Benjamin JS, Chong E, Ramayya MS. A preterm, female newborn with tachycardia, hypertension, poor weight gain, and irritability. *Clin Pediatr (Phila)*. 2012;51(10):994–997

59. Dierickx I, Decallonne B, Billen J, et al. Severe fetal and neonatal hyperthyroidism years after surgical treatment of maternal Graves' disease. *J Obstet Gynaecol*. 2014;34(2):117–122

60. Bisschop PH, van Trotsenburg AS. Images in clinical medicine. Neonatal thyrotoxicosis. *N Engl J Med*. 2014;370(13):1237

61. Dryden C, Simpson JH, Hunter LE, Jackson L. An unusual cause of neonatal coagulopathy and liver disease. *J Perinatol*. 2007;27(5):320–322

62. Trapali C, Dellagrammaticas HD, Nika A, Iacovidou N. A unique case of reversible myocardial ischemia in a hyperthyroid neonate. *Pediatr Cardiol*. 2008;29(1):180–182

63. Aslam M, Inayat M. Fetal and neonatal Graves disease: a case report and review of the literature. *South Med J*. 2008;101(8):840–841

64. Smith CM, Gavranich J, Cotterill A, Rodda CP. Congenital neonatal thyrotoxicosis and previous maternal radioiodine therapy. *BMJ*. 2000;320(7244):1260–1261

65. Beroukhim RS, Moon TD, Felner EI. Neonatal thyrotoxicosis and conjugated hyperbilirubinemia. *J Matern Fetal Neonatal Med*. 2003;13(6):426–428

66. Groom K, Snowise S, Wheeler B, Mekhail A, Farrand S, Parry E. Maternal thyrotoxicosis and fetal goitre requiring in utero therapy for hypothyroidism and subsequent neonatal therapy for hyperthyroidism. *J Paediatr Child Health*. 2013;49(1):E102–E103

67. Bahn RS, Burch HS, Cooper DS, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid*. 2009;19(7):673–674

68. Karras S, Tzotzas T, Krassas GE. Toxicological considerations for antithyroid drugs in children. *Expert Opin Drug Metab Toxicol*. 2011;7(4):399–410

69. Maragliano G, Zuppa AA, Florio MG, et al. Efficacy of oral iodide therapy on neonatal hyperthyroidism caused by maternal Graves' disease. *Fetal Diagn Ther*. 2000;15(2):122–126

70. Zuppa AA, Sindico P, Savarese I, et al. Neonatal hyperthyroidism: neonatal clinical course of two brothers born to a mother with Graves-Basedow disease, before and after total thyroidectomy. *J Pediatr Endocrinol Metab*. 2007;20(4):535–539

71. Angelis D, Kubicky RA, Zubrow AB. Methimazole associated neutropenia in a preterm neonate treated for hyperthyroidism. *Case Rep Endocrinol*. 2015;2015:680191

72. Rivkees SA, Stephenson K, Dinauer C. Adverse events associated with methimazole therapy of graves' disease in children. *Int J Pediatr Endocrinol*. 2010;2010:176970

73. Bahn Chair RS, Burch HB, Cooper DS, et al; American Thyroid Association; American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid*. 2011;21(6):593–646

74. Karpman BA, Rapoport B, Filetti S, Fisher DA. Treatment of neonatal hyperthyroidism due to Graves' disease with sodium ipodate. *J Clin Endocrinol Metab*. 1987;64(1):119–123

75. Kamishlian A, Matthews N, Gupta A, et al. Different outcomes of neonatal thyroid function after Graves' disease in pregnancy: patient reports and literature review. *J Pediatr Endocrinol Metab*. 2005;18(12):1357–1363

76. Kempers MJ, van Tijn DA, van Trotsenburg AS, de Vijlder JJ, Wiedijk BM, Vulsma T. Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. *J Clin Endocrinol Metab*. 2003;88(12):5851–5857

77. Brown RS, Bellisario RL, Botero D, et al. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. *J Clin Endocrinol Metab*. 1996;81(3):1147–1151

78. Higuchi R, Miyawaki M, Kumagai T, et al. Central hypothyroidism in infants who were born to mothers with thyrotoxicosis before 32 weeks' gestation: 3 cases. *Pediatrics*. 2005;115(5). Available at: www.pediatrics.org/cgi/content/full/115/3/e623

79. Lee YS, Loke KY, Ng SC, Joseph R. Maternal thyrotoxicosis causing central hypothyroidism in infants. *J Paediatr Child Health*. 2002;38(2):206–208

80. Brand F, Liégeois P, Langer B. One case of fetal and neonatal variable thyroid dysfunction in the context of Graves' disease. *Fetal Diagn Ther*. 2005;20(1):12–15

81. O'Connor MJ, Paget-Brown AO, Clarke WL. Premature twins of a mother with Graves' disease with discordant thyroid function: a case report. *J Perinatol*. 2007;27(6):388–389

82. Zwaveling-Soonawala N, van Trotsenburg P, Vulsma T. Central hypothyroidism in an infant born to an adequately treated mother with Graves' disease: an effect of maternally derived thyrotrophin receptor antibodies? *Thyroid*. 2009;19(6):661–662

83. Kempers MJ, van Trotsenburg AS, van Rijn RR, et al. Loss of integrity of thyroid morphology and function in children born to mothers with inadequately treated Graves' disease. *J Clin Endocrinol Metab*. 2007;92(8):2984–2991

84. Prummel MF, Brokken LJ, Wiersinga WM. Ultra short-loop feedback control of thyrotropin secretion. *Thyroid*. 2004;14(10):825–829

85. Momotani N, Noh JY, Ishikawa N, Ito K. Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. *J Clin Endocrinol Metab*. 1997;82(11):3633–3636

86. Balucan FS, Morshed SA, Davies TF. Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance. *J Thyroid Res*. 2013;2013:182472

87. McLachlan SM, Rapoport B. Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. *Thyroid*. 2013;23(1):14–24

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