

# Management of Neonates Born to Mothers With Graves' Disease

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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;  $\beta$ -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.

## abstract

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%.<sup>1-4</sup> The prevalence of transient GD in infants born to these mothers is uncertain, varying from 1.5% to 2.5%<sup>5-7</sup> up to 20.0% in observational cohort studies.<sup>7-9</sup>

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.<sup>10</sup> 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.<sup>11</sup>

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.<sup>12,13</sup>

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.<sup>6,11,14–17</sup>

Signs and symptoms of neonatal hyperthyroidism are nonspecific and also could be attributed to congenital viral infections or sepsis.<sup>18</sup> The diagnosis of neonatal hyperthyroidism can therefore be overlooked, resulting in preventable morbidity and mortality, with mortality rates up to 20% reported.<sup>6</sup> Neonatal complication rates are higher in women who remain hyperthyroid during the second half of pregnancy.<sup>19</sup>

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.<sup>20</sup> Similar results were found in 2 other studies.<sup>21,22</sup> 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.<sup>23</sup> Growth in children born to mothers with GD during pregnancy is comparable to unaffected controls.<sup>22,23</sup>

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:

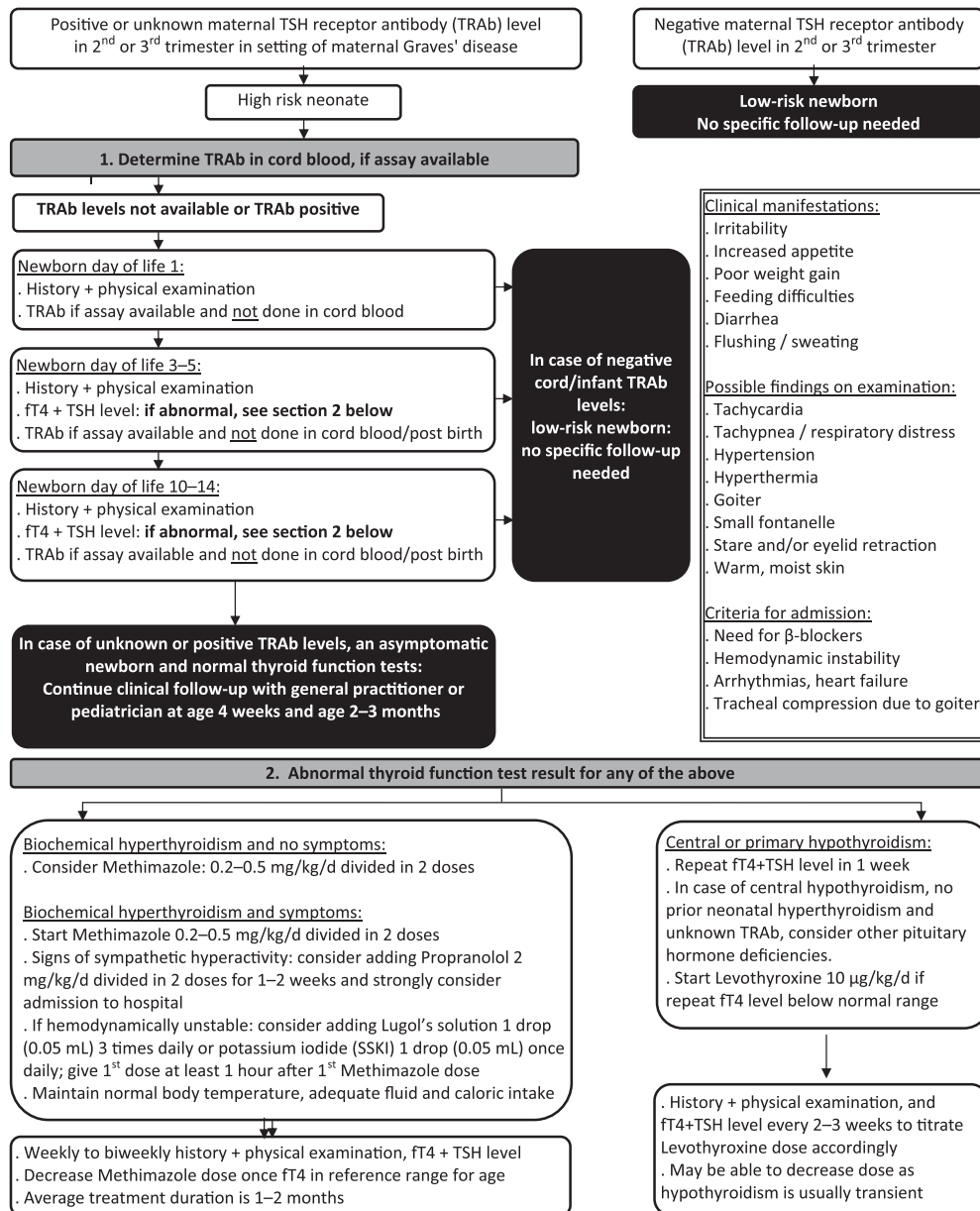
- Is there an association between maternal TRAb levels and risk of neonatal hyperthyroidism?
- Is there utility to determination of TRAb levels in cord blood?
- Are cord blood TSH and fT4 levels valuable in predicting neonatal hyperthyroidism?
- When should TSH and fT4 levels be measured in the “at-risk” 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).<sup>24</sup> 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.<sup>25</sup>

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.<sup>5,26</sup>

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

hyperthyroidism.<sup>7-9,27-33</sup> 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%.<sup>8</sup> 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.<sup>7</sup> In a recent report, none of 35 infants born to mothers with negative TRAb levels during pregnancy developed hyperthyroidism.<sup>9</sup> The risk of neonatal hyperthyroidism after being born to women with negative TRAb levels is therefore regarded as negligible.<sup>34</sup>

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.<sup>35</sup> 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%<sup>35</sup>; 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.<sup>36,37</sup>

*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?**

Skuzza et al<sup>38</sup> 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<sup>9</sup> 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.<sup>9,30,38,39</sup> Positive cord TRAb levels (up to 2.5 times the assay upper reference limit), however, have been reported in newborns with normal thyroid function,<sup>40</sup> 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.<sup>30,38,39</sup> Among 6 newborns who developed hyperthyroidism, Polak et al<sup>40</sup> 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.<sup>9</sup> 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.<sup>9,38,40,41</sup>

In 1 study, ft4 and TSH levels were determined in 96 at-risk newborns during the first month of life.<sup>42</sup> 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.<sup>41-44</sup>

These recommendations for the first 2 weeks of life are consistent with those of others.<sup>6,9,40</sup> After 2 weeks of life, Besançon et al<sup>9</sup> 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.<sup>45</sup> 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.<sup>46</sup> The duration of action of MMI is 36 to 72 hours and of PTU is 12 to 24 hours.<sup>47</sup> 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.<sup>41</sup> 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.<sup>48</sup> 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.<sup>26,49-51</sup> 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<sup>52-54</sup> but not all<sup>1,55,56</sup> studies, and that high-dose PTU treatment has been associated with an increased risk of low birth weight.<sup>3</sup> Because PTU has (rarely) been associated with liver failure in pregnant women,<sup>5,57</sup> current guidelines recommend switching to MMI after the first trimester.<sup>5,26</sup>

#### *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.<sup>38</sup> In 6 patients who were asymptomatic, MMI was initiated at an average ft4 level of 49.6 pmol/L<sup>40</sup> in another report. Besançon et al,<sup>9</sup> who reported mostly on the same cohort as previously published by Polak et al<sup>40</sup> and Luton et al,<sup>30</sup>

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).<sup>9</sup> 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.<sup>9</sup> 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.<sup>14–18,42,58–66</sup> Arguing against this approach is the small series reported by Daneman and Howard<sup>23</sup> 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.<sup>67,68</sup>

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.<sup>11</sup> 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.<sup>18,69–71</sup> 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.<sup>72</sup> 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.<sup>68,72</sup> Serious side effects (0.5% of children) include agranulocytosis, liver injury, vasculitis and Stevens-Johnson syndrome.<sup>68,72</sup> 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.<sup>71</sup>

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.<sup>45</sup>

#### *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.<sup>14,59,64,66,71,73</sup> 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.<sup>74</sup> Depending on the initial TRAb level, neonatal GD generally resolves by 6 months after birth,<sup>35,38,41,75</sup> although 1 instance of persistence to 12 months has been reported.<sup>12</sup> Treatment duration is most commonly 1 to 2 months.<sup>6,9,35,38</sup> 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,<sup>9,14,59</sup> although recent guidelines recommend against this “block and replace” practice.<sup>73</sup> 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.<sup>9,39,76–83</sup> 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.<sup>76</sup> Transient central hypothyroidism,<sup>39,78,79</sup> sometimes followed by hyperthyroidism,<sup>80–82</sup> 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.<sup>76,83</sup> In rare instances, central hypothyroidism can be prolonged and may be permanent.<sup>83</sup>

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.<sup>82,84</sup>

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.<sup>85</sup> 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.<sup>7,33</sup> Primary hypothyroidism can sometimes precede hyperthyroidism.<sup>9</sup> The interplay between TSH-receptor stimulating and blocking antibodies might explain the switch from hypothyroidism to hyperthyroidism and vice versa.<sup>86,87</sup>

#### *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.

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#### **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

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