Clinical Guideline: Management of Babies Born to Mothers with Thyroid Disease

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For use in: EoE Neonatal Units
Guidance specific to the care of neonatal patients.

Used by:

Key Words: Hypothyroidism, thyrotoxicosis, thyroid stimulating immunoglobulin [TSI], TSH-receptor antibody [TRAb], antithyroid drugs [ATD]

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Neonatal Clinical Oversight Group

Clinical Lead Mark Dyke

Ratified

Date of meeting March 2018

Audit Standards:

Audit points
1. All babies at risk of neonatal thyrotoxicosis should have their thyroid function assessed in the first week of life

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Antithyroid drugs</td>
<td>ATD</td>
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<tr>
<td>Free thyroxine</td>
<td>fT4</td>
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<tr>
<td>Thyroid stimulating hormone</td>
<td>TSH</td>
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<tr>
<td>Thyroid stimulating immunoglobulin</td>
<td>TSI</td>
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<tr>
<td>TSH-receptor antibody</td>
<td>TRAb</td>
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Objective:
To guide the management of babies born to mothers with thyroid disease

Rationale:
Thyroid hormones are important for energy metabolism and for the stimulation of growth and development, particularly the brain, in the fetus and newborn. Abnormalities of thyroid function; both hypo and hyperthyroidism, in the neonatal period are associated with significant morbidity including irreversible brain damage.

Autoimmune thyroid disease in the mother caused by thyroid stimulating (TSI) or thyroid blocking immunoglobulins can affect fetal and neonatal thyroid function as these immunoglobulins can cross the placenta. The antithyroid drugs (ATD) used to treat maternal thyrotoxicosis can also cross the placenta and affect fetal and neonatal thyroid function. Thyroid hormone only crosses the placenta in small amounts. The thyroid function in an affected neonate will usually return to normal once the immunoglobulins and drugs are cleared from the baby’s circulation (usually 3-12 weeks but can be more than 36 months [1]). Persistent hyperthyroidism occurs extremely rarely as a familial disorder where there are activating mutations of the thyroid-stimulating hormone (TSH) receptor [2], or in McCune-Albright syndrome [3].

Maternal hypothyroidism:
Hypothyroidism is usually caused by Hashimoto’s thyroiditis. These women have thyroid blocking immunoglobulins which render them hypothyroid. The antibodies can cross the placenta and cause hypothyroidism in the fetus and neonate. Some women will have coexisting thyroid TSI but the risk of neonatal thyrotoxicosis is extremely rare. Congenital hypothyroidism is usually sporadic but can rarely be familial [4].

Maternal thyrotoxicosis
The majority of women with thyrotoxicosis will have Graves’ disease caused by TSI. The risk to the fetus and the neonate is dependent on the TSI level. Some laboratories will measure TSI, however others measure total TSH-receptor antibodies (TRAb) which do not differentiate between thyroid stimulating or blocking antibodies but are very useful for assessing risk to the baby of developing thyrotoxicosis. The higher the maternal TSI or TRAb level in the third trimester of pregnancy, the higher the risk of neonatal thyrotoxicosis [5] which is most likely when the TSI or TRAb is more than three to five times the upper normal limit [6] but can occur at lower levels [7].

Although rare, neonatal thyrotoxicosis has a high mortality rate (up to 25%). Between 1-5% of babies born to mothers with Graves’ disease will develop neonatal thyrotoxicosis; which equates to one case of neonatal thyrotoxicosis for every 10,000-50,000 newborns [8,9]. It is therefore essential to anticipate and monitor for neonatal thyrotoxicosis in at risk babies.

Clinical Features of thyrotoxicosis in the neonate
Symptoms and signs may be present at birth, but are usually delayed for several days, particularly if the mother is taking ATD as these are more rapidly cleared from the baby’s circulation than TSI (TRAb). Clinical features may be delayed for 1-2 months postpartum when coexisting higher affinity blocking antibodies are cleared from the circulation and TSI predominate [10].
Babies may have sub-clinical biochemical thyrotoxicosis. It is unclear as to whether this should be treated. Mild, short-lived biochemical thyrotoxicosis probably can be followed biochemically and clinically. Suggested management in this situation is to treat with ATD if the TSH level is suppressed and fT4 is more than 2 times the upper limit of the normal level for day of age, or persists beyond the first 2 weeks of life.

**Symptoms and signs of neonatal thyrotoxicosis:**
- Small for gestational age (or evidence of intrauterine growth restriction - weight may be within normal range)
- Preterm birth
- Goitre
- Central nervous system signs including irritability and restlessness
- Eye signs including lid retraction, periorbital oedema and proptosis (which can occur even in the absence of maternal eye signs)
- Cardiovascular signs including tachycardia which may progress to tachyarrhythmia and cardiac failure
- Systemic and pulmonary hypertension
- Hypermetabolism presenting as flushing and sweating, avid feeding, diarrhoea, excess weight loss and failure to thrive
- Hepatosplenomegaly
- Lymphadenopathy
- Thrombocytopenia, coagulopathy
- Craniosynostosis and advanced bone age
- Microcephaly
- Frontal bossing
- Jaundice and liver disease

**Management of babies born to mothers with hypothyroidism:**
Babies of mothers with hypothyroidism caused by either Hashimoto’s thyroiditis or congenital hypothyroidism require no investigation apart from ensuring the routine newborn screening is performed. Hypothyroidism in the baby will result in an elevated TSH level and will be picked up on this screen.

Babies born to hypothyroid women who were previously treated with surgery or radioiodine for Graves’ disease are at risk of neonatal thyrotoxicosis, as TSI may persist in mother’s circulation and cross the placenta causing fetal and neonatal hyperthyroidism. These babies should be managed as below and in Figure 1.

**Management of babies born to mothers with a current or past history of Graves’ disease (Figure 1) or where there is a family history of thyrotoxicosis:**

**History:**
- Current / past history of hyperthyroidism
- Family history of thyrotoxicosis (TSH-receptor gene mutations)
- Maternal treatment:
Drugs: Carbimazole or Propylthiouracil. Neonatal thyrotoxicosis is more likely if the mother is taking ATD at term. Both are potentially teratogenic.

- Carbimazole has been associated with choanal atresia, oesophageal atresia, cutis aplasia, abdominal wall defects, eye anomalies, ventricular septal defects and “embryopathy” in 2-4% of exposed children [11-14].
- Propylthiouracil has been associated with minor birth defects, primarily face and neck cysts in 2-3% [12].

- Surgery or radiiodine in the past. Persisting TSI can cause thyrotoxicosis.

Examination:
- Examine for symptoms and signs of neonatal thyrotoxicosis (as above)

Management
- Thyrotoxicosis should be anticipated in high risk babies:
  - those whose mothers have high TSI (TRAb) levels in the third trimester
  - those whose mothers have been clinically thyrotoxic or receiving ATD in the third trimester
  - if there was evidence that the fetus was affected
  - If the TSI (or TRAb) has not been measured, the baby should be considered at high risk.
- Babies at high risk of being missed are those of hypothyroid mothers with a past history of thyrotoxicosis, particularly if she has been treated with radiiodine or thyroidectomy as she may still have high levels of TSI (TRAb) [15].
- If there is a family history of a TSH-receptor mutation, the baby will be at high risk of thyrotoxicosis (50%).

A suggested management plan is depicted in Figure 1
- If the TSI (TRAb) is negative, the mother has been euthyroid and ATD have not been used during pregnancy, the baby does not require formal biochemical follow up unless there are symptoms or signs of thyrotoxicosis.

- If the maternal TSI (TRAb) is unknown, manage the baby as if the TSI (TRAb) were positive.

- If the TSI (TRAb) in the mother is positive, take cord blood for TSH and ideally TSI (TRAb).
  - A suppressed TSH suggests that the fetus has been thyrotoxic and baby needs close monitoring
  - a negative TSI (or TRAb) would negate any further biochemical investigation (unless clinically indicated) but the turnaround time may be too long to be helpful in the management in the first few days of life

- Measure thyroid function (TSH and fT4) at intervals commensurate with the TSI (TRAb) level (either 3rd trimester maternal TSI (TRAb) or cord blood (if rapidly available).
  - Measure thyroid function on day 3-7 in all at risk babies
  - If the TSI (TRAb) is > x3 upper limit of the normal range
- keep the baby under close review for the first few days of life paying particular attention to the heart rate and blood pressure
- repeat thyroid function on day 10-14 or when clinically hyperthyroid [16,17]

- Thyroid function tests in the newborn period need to be interpreted in light of the surge in TSH and T4 that occurs after delivery, giving a different set of normal ranges (see box below).

- Suggested management of abnormal thyroid function tests is shown in Figure 2

- There is no contra-indication to breast feeding [18]

### Thyroid function in the Newborn [19]

<table>
<thead>
<tr>
<th></th>
<th>Term</th>
<th>28-40w gestation</th>
<th>25-30w gestation</th>
<th>31-36w gestation</th>
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<tbody>
<tr>
<td><strong>TSH (mU/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 1</td>
<td>3-120</td>
<td>&gt; Day 7</td>
<td>0.8-12</td>
<td></td>
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<tr>
<td>Day 2</td>
<td>3-30</td>
<td></td>
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<td></td>
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<tr>
<td>Day 3-30</td>
<td>0.5-6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>fT4 (pmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1-3</td>
<td>25.7-68.2</td>
<td>Day 0-7</td>
<td>6.4-42.5</td>
<td>Day 0-7</td>
</tr>
<tr>
<td>Day 4-10</td>
<td>13.7-28.0</td>
<td></td>
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</tbody>
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### References

5. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. Thyroid 1992; 2: 155-159
8. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. Thyroid 1992; 2: 155-159


17. Ogilvy-Stuart AL. Neonatal Thyrotoxicosis. NeoReviews 2017, 18 (7) e422-e430; DOI: 10.1542/neo.18-7-e422


Maternal 3\textsuperscript{rd} trimester TSI (TRAb) negative and no ATD used in pregnancy

Low-risk neonate
No follow-up required

3\textsuperscript{rd} trimester maternal TSI (TRAb) positive / unknown and / or ATD used in pregnancy

Cord blood / postnatal TRAb and TSH
Day 1 history and examination

TSI (TRAb) elevated or unknown
And / or TSH abnormal

Day 3-7
History and examination
TSH + fT4
If abnormal – see Figure 2

TSI (TRAb) < x3 upper limit normal and
TSH + fT4 normal

Day 10-14
History and examination
TSH + fT4 (+ fT3 if available)
If abnormal – see Figure 2

TSI (TRAb) > x3 upper limit of normal

Low-risk neonate
Further investigation if clinically indicated (Letter to GP)

Abbreviations:
TSI: Thyroid stimulating immunoglobulin
TRAb: TSH-receptor antibody
ATD: Antithyroid Drugs
TSH: Thyroid stimulating hormone
fT4: Free thyroxine

Figure 1
Abnormal thyroid function

**Asymptomatic thyrotoxicosis** (suppressed TSH, elevated fT4)
Discuss with Paediatric Endocrinologist
Consider treatment with ATD

**Symptomatic thyrotoxicosis** (suppressed TSH, elevated fT4)
Discuss with Paediatric Endocrinologist
Maintain normal body temperature, fluid and calorie intake
Start ATD
Consider treatment with Propranolol if sympathetic hyperactivity
Start treatment with iodine if severe thyrotoxic symptoms
Treat heart failure if present
Consider corticosteroids if severely thyrotoxic

Regular clinical review and measurement of TSH, fT4:
Biweekly initially, then weekly, then alternate weeks once stable
Wean and then discontinue ATD once thyroid

**Primary hypothyroidism** (elevated TSH, low fT4) or
**Central hypothyroidism** (low fT4, low/normal TSH)

Biochemical thyrotoxicosis

Euthyroid

Persisting hypothyroidism

Consider clinical and biochemical follow-up in 2-3 weeks to screen for emerging thyrotoxicosis

Discuss with Paediatric Endocrinologist:
Treat with thyroxine
Monitor clinically and biochemically 2-3 weekly to titrate thyroxine dose and screen for emerging thyrotoxicosis

**Abbreviations:**
ATD: antithyroid drugs
TSH: thyroid stimulating hormone
fT4: Free thyroxine

Figure 2
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<th>Signature of Trust Nursing / Medical Director:</th>
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