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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Approved by:

Neonatal Clinical Oversight Group	
Clinical Lead Matthew James	**Matthew James**

Ratified

Date of meeting	

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

Antithyroid drugs	ATD
Free thyroxine	fT4
Thyroid stimulating hormone	TSH
Thyroid stimulating immunoglobulin	TSI
TSH-receptor antibody	TRAb

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 co-existing 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 tachyarrythmia 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]
  - Prophylthyrouracil has been associated with minor birth defects, primarily face and neck cysts in 2-3% [12].
- Surgery or radioiodine 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 **hypo**thyroid mothers with a past history of thyrotoxicosis, particularly if she has been treated with radioiodine 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 (or 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]

Normal ranges in infants (19)	TSH (mU/L)	FreeT4(pmol/L)	Free T3 (pmol/L)
Term: Cord blood to 48hrs	3-120	16.7-48.3	2.5-9.3
Term: at 4 -10 days postnatally	0.3-6	13.7-28	2.8-5.7
28-36 weeks: Cord blood to 48 hrs	0.7-27	11.3-24	1.2-7.3
28-36 weeks:4-10 days postnatally	0.7-27	10-30	1.2-4.9

It is common to find TSH and free T4 are both raised in the first few days of life. This is a normal acute phase response and is not hyperthyroidism. Thyrotoxicosis features suppressed TSH. One in 70 babies whose mother has Graves' disease develops Neonatal Thyrotoxicosis, but there can be significant morbidity and risk of mortality.

The decision of whether to treat is complex. All cases where treatment is considered must be discussed with a Paediatric Endocrinologist.

- Infants with raised fT4 and suppressed TSH: significant biochemical abnormalities indicate thyrotoxicosis but treatment (carbimazole alone) will depend on the presence of clinical signs

- Infants with abnormal biochemistry and adrenergic clinical signs: tachycardia, wakefulness, tachypnoea should be treated with carbimazole and propranolol. Consider referral as below.

- Infants with evidence of actual or incipient cardiac failure: should be referred to a Paediatric Endocrinology Team. As well as carbimazole and propranolol, consideration should be given to Lugol's iodine and rarely prednisolone.

Drug Therapy Options

- Carbimazole: 250 micrograms/kg 3 times daily (severe thyrotoxic crisis may require higher dose). Blocks thyroid hormone synthesis by preventing organification and coupling of iodothyronine residues, but doesn't inhibit the release of preformed thyroid hormones.

- Propranolol: 250–500 micrograms/kg every 8 hours. Helps control symptoms due to adrenergic stimulation and inhibits T4 to T3 de-iodination.

- Lugol's Iodine solution (rare): 1 drop 3 times daily. Usual duration 3 days, max 7. Promptly blocks preformed thyroid hormone release and reduces thyroid hormone synthesis.

- Prednisolone (rare): 2mg/kg/day. Inhibits thyroid hormone release and inhibits peripheral conversion of T4 to T3.

Prognosis

Excessively high dose of prolonged use of antithyroid treatment can lead to subsequent period of thyroid suppression ie hypothyroidism. Ensure 2 normal TFTs after withdrawal of treatment.

Rarely (if severe / prolonged duration of many months), there is a risk of craniosynostosis and developmental delay, so monitor head circumference growth and development in those cases.

Progress and Monitoring

- Aim is to abolish hyperthyroidism without causing hypothyroidism.
- Titrate treatment against clinical response. Stop propranolol once clinically euthyroid.
- Measure TFTs fortnightly. If fT4 in normal range, then reduce carbimazole dose by 25%. (TSH suppression often shows a 2-3 week lag, so don't wait for that in order to reduce dose).
- Continue this consideration of dose reduction according to TFTs fortnightly.
- Maternal antibodies have approximately a 6 week half-life. Treatment may be needed for 8-12 weeks.
- FBC should be performed if clinical evidence of infection, not routinely (carbimazole may cause agranulocytosis in 0.03% of patients).

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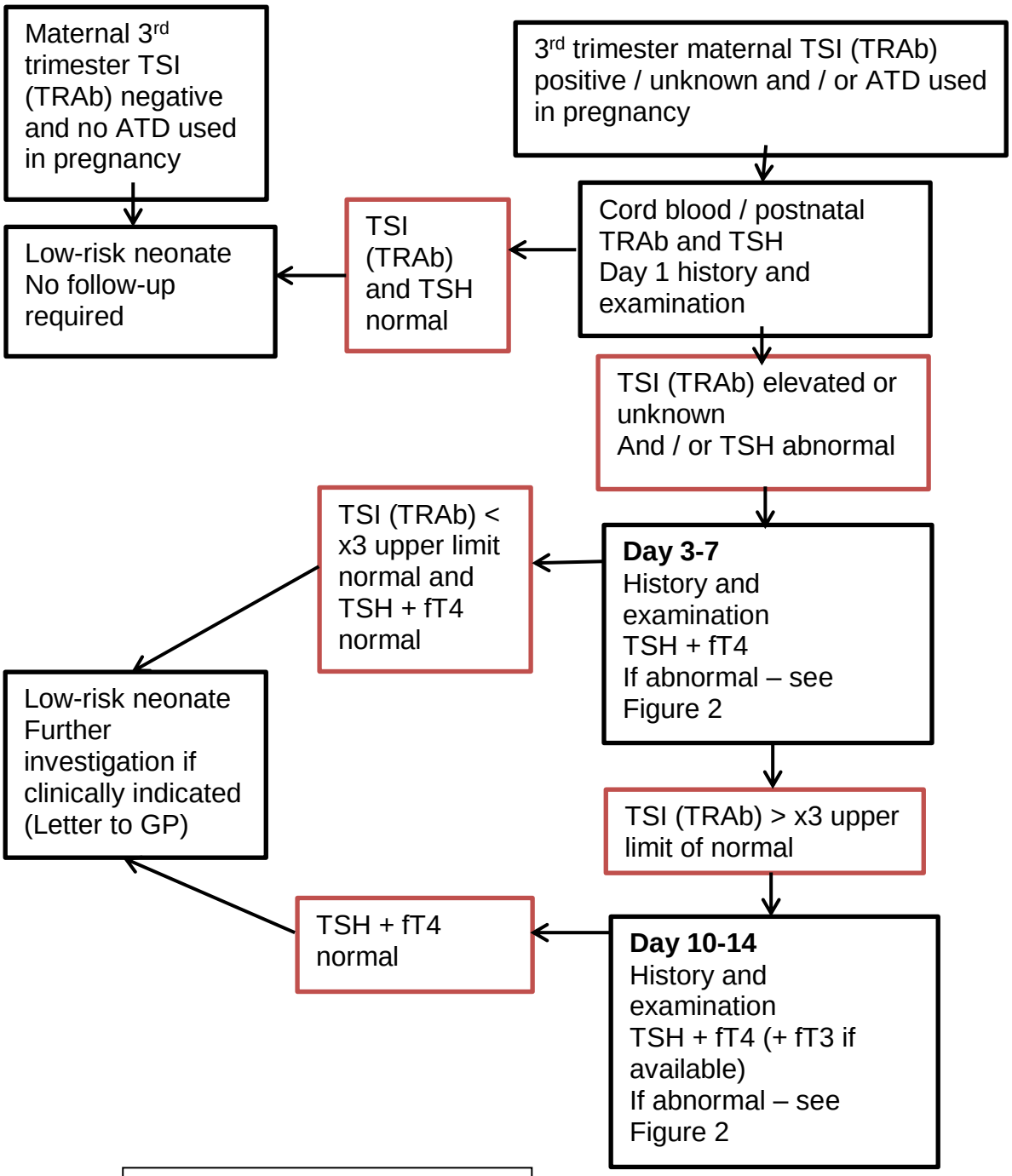
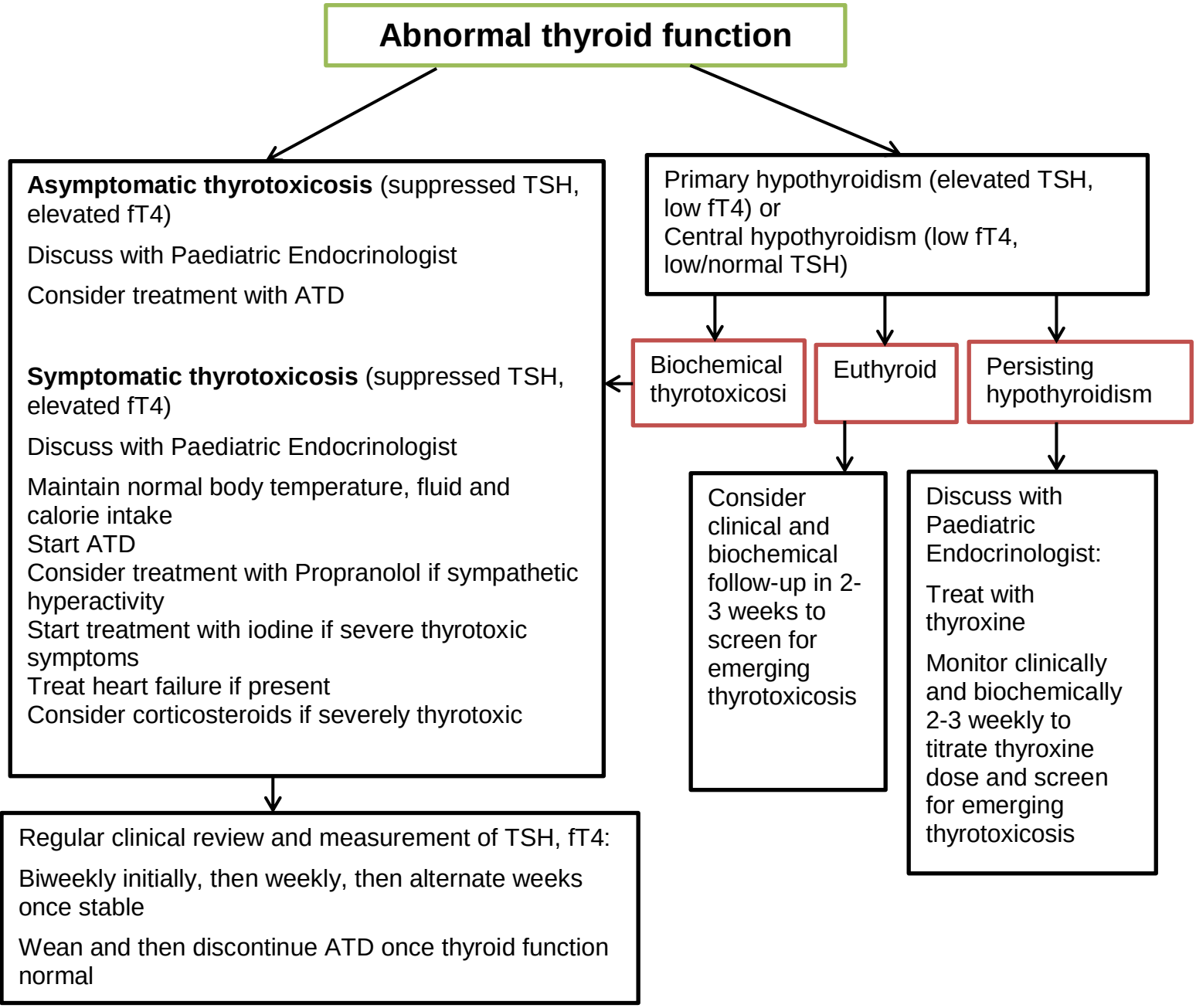


Abbreviations:
TSI: Thyroid stimulating immunoglobulin
TRAb: TSH-receptor antibody
ATD: Antithyroid Drugs
TSH: Thyroid stimulating hormone
fT4: Free thyroxine

Figure 1



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

Figure 2

East of England Neonatal ODN
(Hosted by Cambridge University Hospitals)

Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

Details of person completing the form:	
Title:	Organisation:
First name:	Email contact address:
Surname:	Telephone contact number:
Title of document to be excepted from:	
Rationale why Trust is unable to adhere to the document:	
Signature of speciality Clinical Lead: Date:	Signature of Trust Nursing / Medical Director: Date:
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