Scottish Paediatric Endocrine Group (SPEG)

Management of infants born to mothers with Graves' disease and at risk of Thyrotoxicosis

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

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Purpose of guideline

Management of infants born to Mothers with Graves' disease.

Who should use this guideline?

- General Paediatricians
- Neonatologists
- Paediatric endocrinologists
- Midwifery staff
- Neonatal unit Staff
- Foetal Medicine Teams

To whom this guideline applies

All infants of women with active or historic Graves' disease, including women who have undergone definitive treatment of Graves' disease.

Acknowledgement

SPEG gratefully acknowledges the Division of Endocrinology based at The Hospital for Sick Children, Toronto and the Departments of Paediatrics and Physiology at The University of Toronto, Ontario, Canada for much of this guideline is based on their published work.

Summary of guideline

Identification of at-risk babies

Based on maternal history and measurement of maternal TRAb (Thyroid receptor antibody) in the 2nd or 3rd trimester.

Investigations

- Birth: Cord blood for TRAb level and fT_4 + TSH if clinically indicated
- Day 1: TRAb if not done on cord blood
- Day 3-5: fT_4 + TSH + T_3 (TRAb if not done on cord blood)
- Day 10-14: fT_4 + TSH + T_3 (TRAb if not done on cord blood)

Treatment

If thyroid function is abnormal at any point above:

- **first line therapy**
  - Carbimazole: 0.750mg/kg/day in single or divided doses until euthyroid, then adjust dose as necessary (as per cBNF 2017)

- **adjunct therapy:**
  - sympathetic overactivity – propranolol 2mg/kg/day in 3 or 4 divided doses
  - haemodynamically unstable – Iodine solution 0.05ml TDS for 1 week

Introduction

The prevalence of maternal hyperthyroidism due to Graves' disease in pregnancy varies from 0.1% to 2.7%. The prevalence of subsequent, transient neonatal Graves' disease is uncertain, varying from 1.5% to 20% in some studies.
Foetal thyroid development is in progress by week 7 gestation, thyroid hormone synthesis begins in weeks 10-12 and the thyroid is functionally mature by week 25.
The causal antibodies in Graves' disease, thyroid stimulating hormone (TSH) receptor antibodies (TRAb) freely cross the placenta, particularly in the second half of pregnancy thus putting the developing foetus at risk of hyperthyroidism.
Infants with hyperthyroidism may present in utero, usually in the 3rd trimester with signs that include tachycardia, heart failure with non-immune hydrops, IUGR, preterm birth and craniosynostosis.

Identification of infants at risk of Hyperthyroidism

Any infant whose mother has an active or historic diagnosis of hyperthyroidism or any mother with a previous infant with neonatal hyperthyroidism is potentially at risk of thyrotoxicosis.

Any infant whose mother has positive TRAb during pregnancy.

Recommendation

For these women, maternal TRAb levels should be determined between 20-24 weeks gestation.

Maternal TRAb negative – no specific follow-up necessary.
Maternal TRAb positive or unavailable – consider infant high risk of thyrotoxicosis.

Examination of at-risk infants

Foetal hyperthyroidism is most seen during the 3rd trimester. In symptomatic cases, foetal hyperthyroidism may be treated by administration of antithyroid drugs (ATD) to the mother.

Neonatal signs and symptoms may be present at birth or delayed for several days, particularly in the presence of maternal ATD treatment.

It is reported that >95% of infants who develop symptoms do so between 1 and 29 days of life with the majority being diagnosed in the first 2 weeks of life.

Recommendation

All high-risk babies should be examined on day 1 of life, day 3-5 and day 10-14, looking for evidence of hyperthyroidism (see Table 1 below).

Babies should be reviewed more frequently if there is any clinical concern.
Criteria for considering admission to hospital:

- need for β-blocker
- heart failure, arrhythmia
- haemodynamic instability
- tracheal compression secondary to goitre
- failure to thrive

Table 1: Clinical features of thyrotoxicosis

Foetal signs and symptoms
• CVS - Tachycardia, arrhythmias, non-immune hydrops • Antenatal Scan - hyperkinesis, IUGR, goitre, advanced bone age • Preterm delivery • Death in utero
Neonatal signs and symptoms
• Goitre • CVS - tachycardia, arrhythmia, failure, hypertension • Respiratory - tachypnoea, respiratory distress, pulmonary hypertension • Neurology - irritability, jitteriness, restlessness • Metabolic - hyperthermia, sweating, flushing, weight faltering, • GI – increased appetite, diarrhoea, jaundice, hepatosplenomegaly • Eyes - stare, eyelid retraction, peri-orbital oedema, exophthalmos • Craniosynostosis, microcephaly • Haematology - Bruising, petechial, thrombocytopenia

Investigations

Levels of TRAb in cord blood should be determined as soon as possible to allow discharge of infants with negative antibodies.

Determination of thyroid function from the cord is not indicated as there is no evidence to suggest that these levels predict neonatal hyperthyroidism.

In infants considered high risk, repeat thyroid function testing, in addition to physical examination is recommended.

Recommendation

Blood tests to be carried out as follows:

- Delivery: Cord blood for TRAb only
- Day1: TRAb if not done from cord blood
- Day 3-5: fT_4 and TSH
- Day 10-14: fT_4 and TSH

Management of infants with Hyperthyroidism

Positive or unknown TRAb with normal thyroid function in an asymptomatic infant requires follow up age 4 weeks and 2-3 months.

Positive or unknown TRAb with abnormal thyroid function requires assessment of clinical features and likely treatment with antithyroid drugs (ATD).

The aim of treatment in symptomatic infants is to facilitate return to biochemical euthyroid state.

Treatment should be initiated at the onset of symptoms to avoid short- and long-term complications.

There is no clear evidence that biochemical hyperthyroidism in the absence of symptoms should be treated.

This should be a decision made by the relevant consultant and endocrine team.

Early discussion with the local endocrine team is essential. All infants who are hyperthyroid should be discussed with the local endocrine team.

Recommendation

- **Biochemical hyperthyroidism in a symptomatic infant**
  - start carbimazole 0.750mg/kg/day in single or divided doses
  - use propylthiouracil 2.5 to 5mg/kg twice daily instead of carbimazole if there are significant side effects with carbimazole

- **Biochemical hyperthyroidism in asymptomatic infant**
  - consider carbimazole: 0.2-0.750mg/kg/day in single or divided doses (but this may not be necessary if the infant remains asymptomatic)

- **Signs of sympathetic hyperactivity:**
  - consider adding Propranolol 2mg/kg/day in 3 to 4 divided doses (+/- admission to hospital)

- **Haemodynamically unstable:**
  - infants should be admitted, and management discussed with local endocrine team.
  - Iodine solution (Lugol's solution) 1 drop (0.05ml) TDS

Table 2: Adverse Effects of medication

Carbimazole	
Mild	Serious
• Transient liver transaminitis • Transient leucopenia • Skin rashes • GI upset • Arthralgia, myalgia	• Agranulocytosis – fever, mouth ulcers, neutropenia • Liver injury • Vasculitis • Stevens-Johnson syndrome

Follow-up of infants with Hyperthyroidism

Neonatal hyperthyroidism due to maternal Graves' disease is self-limiting, with duration determined by the rate of disappearance of maternal TRAb from infant circulation. TRAb half-life is reported to be approximately 12 days.

- **Monitoring**
  - weekly to biweekly review and thyroid function tests depending on clinical condition of the infant.
  - taper treatment once asymptomatic and fT_4 and TSH is within the reference range

- **Prognosis**
  - average treatment duration is 1-2 months
  - Hyperthyroidism generally resolves within 6 months but can continue for up to 12 months.
  - once thyroid function has normalised off treatment, no further review is required.
  - there is a risk of recurrence in siblings in future pregnancies

Maternal Hypothyroidism

Infants of mothers with primary hypothyroidism are generally not at risk of hypothyroidism.

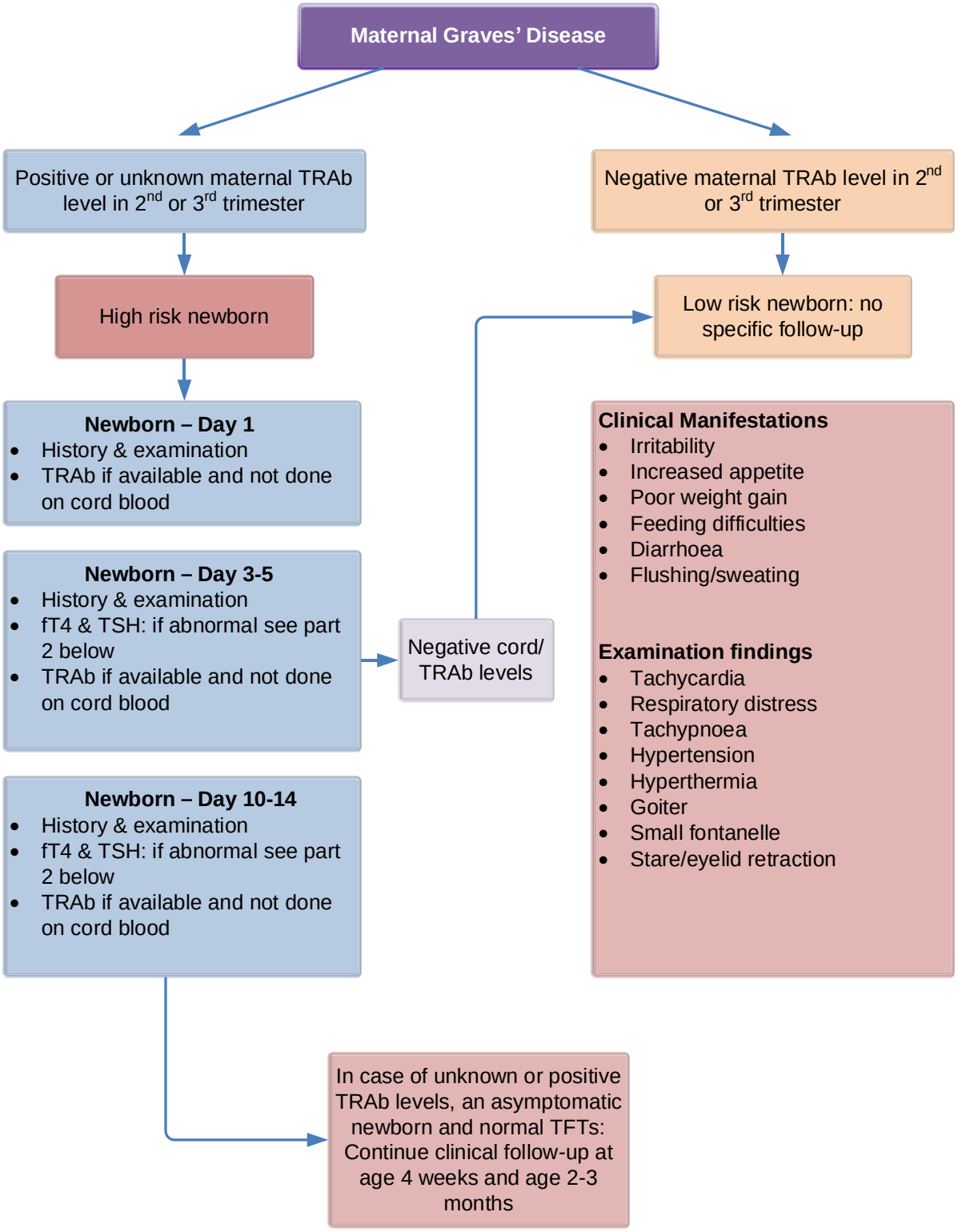
These infants will normally have their TSH checked at day 5 as part of the newborn screening programme.

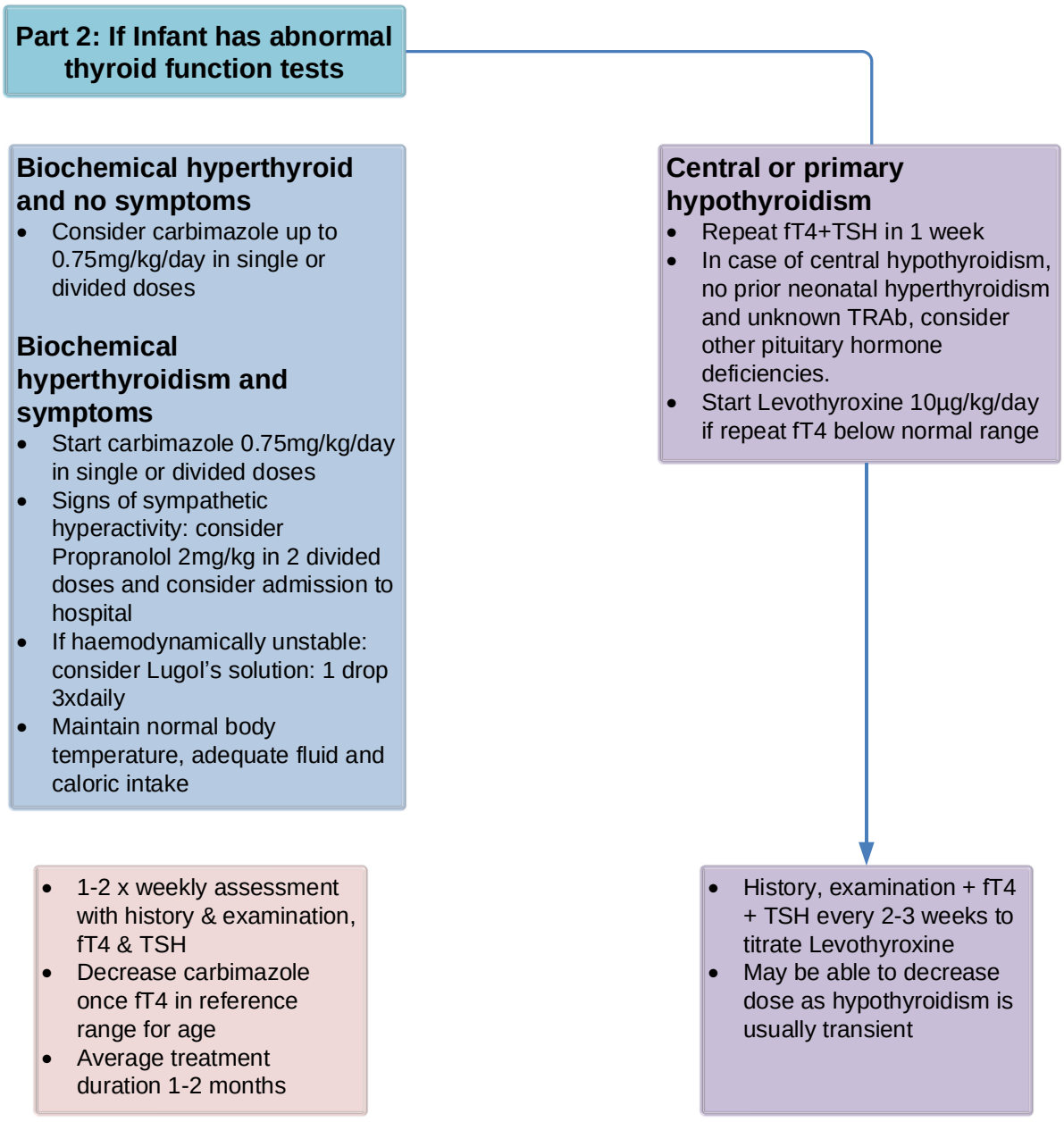
No further testing is generally required.

Caution should be exercised if the cause of the maternal hypothyroidism is unknown, as the mother may have been treated for hyperthyroidism previously and had become hypothyroid.

If in doubt it is wise to assume the mother may have been hyperthyroid and that the mother may have thyroid antibodies.

Flowchart for Management of Neonatal Thyrotoxicosis




Part 2: If Infant has abnormal thyroid function tests
Biochemical hyperthyroid and no symptoms
Consider carbimazole up to 0.75mg/kg/day in single or divided doses
Biochemical hyperthyroidism and symptoms
Start carbimazole 0.75mg/kg/day in single or divided doses
Signs of sympathetic hyperactivity: consider Propranolol 2mg/kg in 2 divided doses and consider admission to hospital
If haemodynamically unstable: consider Lugol's solution: 1 drop 3xdaily
Maintain normal body temperature, adequate fluid and caloric intake
1-2 x weekly assessment with history & examination, fT4 & TSH
Decrease carbimazole once fT4 in reference range for age
Average treatment duration 1-2 months
Central or primary hypothyroidism
Repeat fT4+TSH in 1 week
In case of central hypothyroidism, no prior neonatal hyperthyroidism and unknown TRAb, consider other pituitary hormone deficiencies.
Start Levothyroxine 10µg/kg/day if repeat fT4 below normal range
History, examination + fT4 + TSH every 2-3 weeks to titrate Levothyroxine
May be able to decrease dose as hypothyroidism is usually transient

Laboratory reference ranges for thyroid function

It is important to check the local laboratory reference ranges as these will vary across Scotland, due to the different assays currently in use.

References

1. van der Kay D.C., Wasserman J.D & Palmert M.R. Management of Neonates Born to Mothers with Graves' Disease. Pediatrics. 2016 Apr;137(4). pii: e20151878
2. Banakar, M.K. & Formosa, M. Serum Thyroid Function Tests in Neonates of Mothers with Thyroid Disease. Indian J Pediatr (2011) 78: 870. doi:10.1007/s12098-010-0337-1
3. Management of Fetal and Neonatal Graves' Disease Juliane Léger. Horm Res Paediatr 2017;87:1–6
4. Children's BNF, latest version (2017)