Management of Infants of Mothers with Thyroid Conditions

Guideline Responsibilities and Authorisation

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Guideline Review History

Version	Updated by	Date Updated	Summary of Changes

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1 Overview

1.1 Purpose

The purpose of this document is to familiarise health professionals to the potential risks for infants born to mothers with thyroid disorders, to identify and screen infants who are at risk of developing thyroid dysfunction due to maternal thyroid disease, and provide guidance on follow-up requirements. In particular it is important to identify infants at risk of the rare but serious disorder neonatal autoimmune hyperthyroidism (neonatal Graves' disease).

1.2 Staff group

Health NZ Waikato medical, midwifery and nursing staff, including obstetric, and neonatal who are involved with the care of newborn infants.

1.3 Patient / client group

Neonates

1.4 Definitions and acronyms

Fetal Growth Restriction (FGR)	Classification of FGR Customised *BW < 3rd centile **or** customised *BW ≥ 3 to < 10 centile **and** ≥ 2 of: • BMI z-score < -1.3 • length z-score < -1.3 • skin/body fat z-score < -1.3 (where equipment and expertise allow) • antenatal FGR diagnosis • major FGR risk factor • placental insufficiency on histology **or** customised *BW ≥ 10 centile, antenatal FGR diagnosis and evidence of placental insufficiency (Abnormal Dopplers)
NNT	Neonatal Team
NST	National Screening Test
TFT	Thyroid function test (T4 (free), T3 (free), TSH)
TPO antibodies	Thyroid antibodies or thyroid peroxidase antibodies
TRAb's	TSH Receptor Antibodies (= TSI)
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone
TSI	Thyroid stimulating immunoglobulins (specific to Grave's disease)

2 Background

2.1 Maternal Hyperthyroidism

Hyperthyroidism affects 0.1-0.4% of pregnancies and the most common aetiologies are autoimmune hyperthyroidism (Graves' disease) (95%), and gestational transient hyperthyroidism (1-3%) (Reference 4).

Neonatal autoimmune hyperthyroidism (neonatal Graves' disease) affects about 2% of infants of mothers who have autoimmune hyperthyroidism (Graves' disease) (Ref 1). It is caused by TSH receptor antibodies that have crossed the placenta leading to clinical symptoms in the foetus and neonate. It can occur in babies of mothers with active disease or those who have been treated in the past but still have circulating antibodies.

It is important to remember that mothers who have had a past history of autoimmune hyperthyroidism can become hypothyroid following treatment, and then require thyroxine. These mothers can still have circulating antithyroid antibodies. Infants of these mothers are also at risk of neonatal autoimmune hyperthyroidism.

2.2 Features of fetal and neonatal hyperthyroidism

Foetus
Features in the foetus include goitre, FGR, oligohydramnios, tachycardia, hydrops (associated with heart failure), increased risk of fetal compromise.

Neonate
In the neonate symptoms can present in the first few days and may last 3-6 months proportional to the clearance of maternal transplacentally acquired antibodies. There can be delayed presentation in babies of treated mothers due to the effects of transplacentally transferred maternal antithyroid drugs or blocking antibodies. Neonatal features can include goitre, irritability, restlessness, excessive weight loss, failure to thrive, diarrhoea, sweating, flushing, eye signs (peri-orbital oedema, lid retraction, proptosis), tachycardia, cardiac failure, advanced bone age, craniosynostosis, microcephaly, hepatosplenomegaly, thrombocytopenia, hyperviscosity.

When assessing a neonate it is important to appreciate that these features can be non-specific and a range of differential diagnoses need to be considered including sepsis, hypoglycaemia, drug withdrawal, and other causes for cardiorespiratory compromise.

2.3 Maternal Hypothyroidism

The most common cause of primary hypothyroidism in reproductive age is chronic autoimmune hypothyroidism (Hashimoto's thyroiditis). There may be circulating **stimulating** or **inhibiting** antibodies that may transiently affect the neonate. There is a very small risk of hypothyroidism in the baby and this will be picked up by the routine newborn metabolic screen (NST – national screening test).

There are significant alterations in thyroid function during pregnancy and increased dietary iodine requirements. Iodine, TRH, antithyroid medications and most maternal thyroid hormones, and IgG antibodies cross the placenta and yet there is no transplacental passage of TSH (Ref 4). Levothyroxine therapy may be required for treatment of maternal

hypothyroidism and this crosses the placenta protecting the foetus from hypothyroidism until postpartum (Ref 4). It is of course essential to optimise the maternal management in pregnancy to prevent any risk to the foetus of hypothyroidism.

2.4 Physiological Changes in the Newborn

There is a natural physiological surge in TSH peaking at about 30 minutes after birth and then reducing to normal term levels by 3-5 days. The TSH surge stimulates neonatal T4 production which peaks by 48 hours after birth with normalisation of T4 (free) levels over several weeks (Ref 6). For this reason it is important to interpret any thyroid function results in context of the clinical history and age of the baby. For example a marginal raised T4 (free) in a 5 day old asymptomatic baby may reflect the physiological changes in T4 (free) rather than neonatal hyperthyroidism. The optimal timing of thyroid function tests in the newborn is debatable.

2.5 History

It is very helpful to have a detailed maternal history.
Specific to the maternal thyroid history it is valuable to have the following information:

Maternal diagnosis

- Graves' disease (Autoimmune hyperthyroidism) YES or NO
- Hashimoto's Thyroiditis (Autoimmune hypothyroidism) YES or NO
- Other maternal thyroid disorders e.g.….aplasia, ectopic, post thyroidectomy for Ca, genetic disorders

Maternal Treatment

- Anti-thyroid drugs
- Thyroxine
- Past thyroid surgery

Maternal TSI antibody levels

- Note maternal TSI antibody values
- Plan for management or the baby should be documented during the antenatal period

One of the most common scenarios is that of a mother who has been on thyroxine but the specific diagnosis and TSI antibody status is unknown. This makes it difficult to assess the risk to the infant and determine the need for any further investigations. For such infants, consideration should be given to test cord blood for TSI antibodies.

Note: Waikato Hospital laboratory does TSI receptor antibodies in batches, with a potential long turnaround time up to 3 weeks. - TSI antibody testing cannot be performed urgently.

3 Clinical management

3.1 Roles and responsibilities

3.1.1 Antenatal Care Providers (LMC, Obstetric team)

Antenatal and delivery planning

- Recommend LMC refers for consultation to obstetric team if maternal history of hyperthyroidism
- Obstetric team to document ongoing management, including
  - Investigations: e.g. thyroid function tests, thyroid antibody studies (TSI)
  - Treatment: e.g. antithyroid medication, any surgery such as thyroidectomy
  - Clarify the postnatal management plan as part of the pregnancy and delivery planning, review this guideline and consult with the neonatal team (NNT) if needed

Postnatal management of newborn

Recommend the LMC does the initial clinical review, NNT to provide a clinical review of the baby in the postnatal period if requested by the LMC or midwife.

All babies born with maternal or family history with risk factors for the baby, e.g. Graves' disease are recommended to have a consultation with neonatal services.

3.2 Testing

3.2.1 Maternal Investigations

- Thyroid function tests TSH, T4 (free)
- Thyroid antibodies or TPO (thyroid peroxidase) antibodies

  Reference Interval (current): ≤ 35 IU/mL
- TSH Receptor Antibodies or TSI Thyroid-Stimulating Immunoglobulin (Grave's disease specific)
- TSH receptor antibodies requires a serum sample (gold top/red top tubes).

  Reference Interval (current): ≤ 2.0 IU/L

Any thyroid function tests particularly antibodies (TSI) done during 2nd or 3rd trimester are very helpful as the presence of thyroid receptor antibodies at this time increase the risk for neonatal hyperthyroidism.

The Waikato Hospital laboratory uses the term **TSI** for the thyroid stimulating antibodies and these are the antibodies we are particularly interested in as they are associated with an increased risk of neonatal **hyperthyroidism**.

3.2.2 Newborn investigations

LMC to arrange thyroid function tests on the baby as per the flow chart (Appendix B) and consult with the neonatal team if the results are abnormal.

For infants of mothers with Graves' disease

- Request TSH, T3 (free), T4 (free) on Day 5-7 (Appendix A for sample blood form)
- If the mother has been on antithyroid medication arrange for baby to have repeat TFTs (T4 (free), TSH) on Day 10-14.
- A follow-up clinical review by the LMC at 7-14 days. This is because there can be a delayed presentation of hyperthyroidism in this clinical scenario.
- If there is a need to test for TSH Receptor Antibodies or TSI Thyroid-Stimulating Immunoglobulin (Grave's disease specific), please also send a serum sample (gold top/red top tubes). Reference Interval (current): ≤ 2.0 IU/L.

For all other thyroid problems (including maternal hypothyroidism)

- no routine TFTs required, but ensure NST is sent

If results suggest hyperthyroidism, then consult with neonatal SMO and consider Paediatric Endocrinology opinion regarding further management.

a) If baby asymptomatic, the results will gradually normalise over a few months and can be monitored at a frequency decided by the responsible clinician. A suggested approach is fortnightly TFTs for a month and then monthly until levels normalise.

b) If baby is symptomatic, then recommend early consult with Paediatric Endocrinology as baby may require antithyroid medications if symptoms are moderate to severe. Infants with mild symptoms can still be monitored with serial TFTs as per the asymptomatic infant above. Treatment with antithyroid drugs is rarely needed as symptoms improve as the transplacentally acquired antibody levels reduce.

It is recommended that if baby has clinical signs of hyperthyroidism, consult with NNT regarding management. The neonatal team can determine whether Paediatric Endocrine opinion is required.

If any clinical signs of hyperthyroidism (see section 2.2 Features of fetal and neonatal hyperthyroidism) consider early TFTs (T4 [free], TSH) with understanding that there is usually a TSH surge shortly after delivery and results should be interpreted with consideration for the age of the baby.

Congenital Hypothyroidism

Refer to the Starship guideline for initial management as well as ongoing monitoring.

Congenital Hypothyroidism - early assessment and management (starship.org.nz)

- Weekly TSH & T4 until TSH normalises
- Twice weekly TSH & T4 thereafter
- Aim for TSH in normal range and T4 in upper 2/3rds of normal

- Once infant is 12 months of age, frequency of testing can be dropped to 2-monthly OR as directed by Paediatric Endocrinologist

Positive NTC results will be communicated to Paediatrician with special interest in endocrinology at Health NZ Waikato via email by the SMO initiating management.

Treatment decisions in very mild or borderline cases can be difficult and should ideally be made in conjunction with Paediatrician with special interest in endocrinology at Health NZ Waikato or if unavailable the on-call Starship paediatric endocrinologist.

Referral to general paediatrics at Health NZ Waikato for long-term management

4 Evidence base

4.1 Bibliography / References

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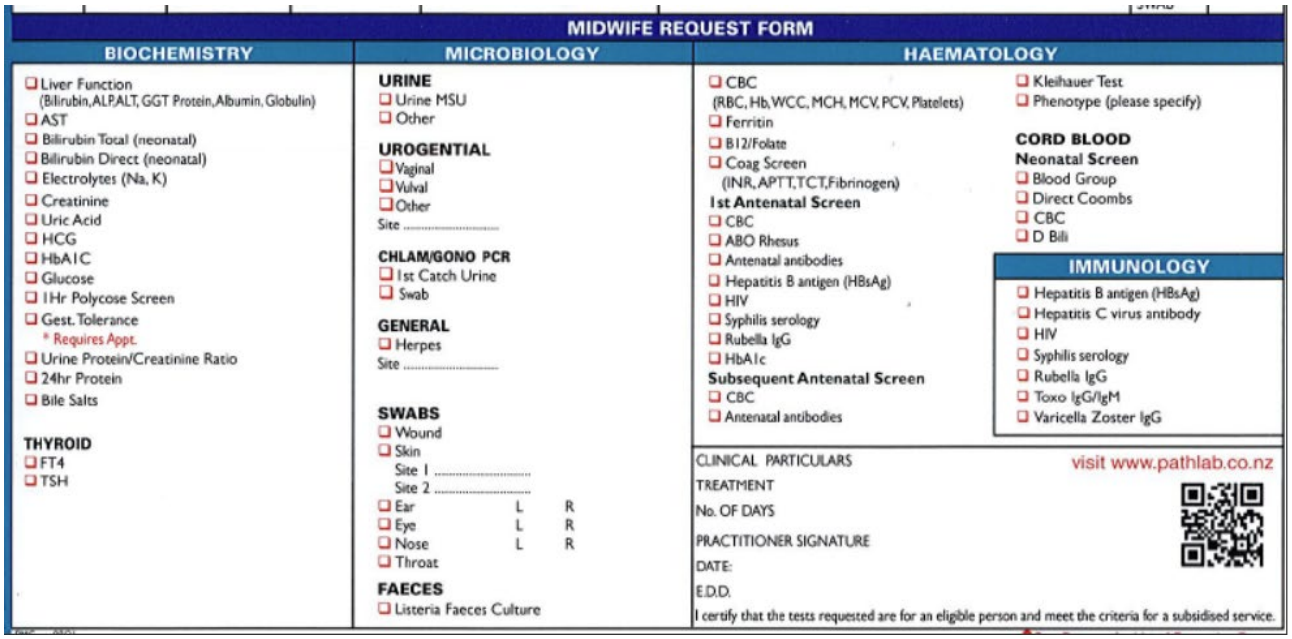
- Thyroid New Zealand website www.thyroidnz.nz
- Laboratory test Guide - https://lab.waikatodhb.health.nz/test-guide/

Appendix A – Sample Blood Test Form



MIDWIFE REQUEST FORM

BIOCHEMISTRY

- ❑ Liver Function (Bilirubin, ALP, ALT, GGT Protein, Albumin, Globulin)
- ❑ AST
- ❑ Bilirubin Total (neonatal)
- ❑ Bilirubin Direct (neonatal)
- ❑ Electrolytes (Na, K)
- ❑ Creatinine
- ❑ Uric Acid
- ❑ HCG
- ❑ HbA1C
- ❑ Glucose
- ❑ 1Hr Polycose Screen
- ❑ Gest. Tolerance
  * Requires Appt.
- ❑ Urine Protein/Creatinine Ratio
- ❑ 24hr Protein
- ❑ Bile Salts

THYROID

- ❑ FT4
- ❑ TSH

MICROBIOLOGY

URINE

- ❑ Urine MSU
- ❑ Other

UROGENTIAL

- ❑ Vaginal
- ❑ Vulval
- ❑ Other

Site .....

CHLAM/GONO PCR

- ❑ 1st Catch Urine
- ❑ Swab

GENERAL

- ❑ Herpes

Site .....

SWABS

- ❑ Wound
- ❑ Skin

Site 1 .....
Site 2 .....

- ❑ Ear L R
- ❑ Eye L R
- ❑ Nose L R
- ❑ Throat

FAECES

- ❑ Listeria Faeces Culture

HAEMATOLOGY

- ❑ CBC (RBC, Hb, WCC, MCH, MCV, PCV, Platelets)
- ❑ Ferritin
- ❑ B12/Folate
- ❑ Coag Screen (INR, APTT, TCT, Fibrinogen)

1st Antenatal Screen

- ❑ CBC
- ❑ ABO Rhesus
- ❑ Antenatal antibodies
- ❑ Hepatitis B antigen (HBsAg)
- ❑ HIV
- ❑ Syphilis serology
- ❑ Rubella IgG
- ❑ HbA1c

Subsequent Antenatal Screen

- ❑ CBC
- ❑ Antenatal antibodies

- ❑ Kleihauer Test
- ❑ Phenotype (please specify)

CORD BLOOD

Neonatal Screen

- ❑ Blood Group
- ❑ Direct Coombs
- ❑ CBC
- ❑ D Bili

IMMUNOLOGY

- ❑ Hepatitis B antigen (HBsAg)
- ❑ Hepatitis C virus antibody
- ❑ HIV
- ❑ Syphilis serology
- ❑ Rubella IgG
- ❑ Toxo IgG/IgM
- ❑ Varicella Zoster IgG

CLINICAL PARTICULARS

visit www.pathlab.co.nz

TREATMENT

No. OF DAYS

PRACTITIONER SIGNATURE

DATE:

E.D.D.

I certify that the tests requested are for an eligible person and meet the criteria for a subsidised service.

Appendix B – Flowchart for Infants of Mothers with Grave's Disease.