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Background

Thyroid hormones are critical for brain and somatic development in infants and for regulation of metabolic activity in adults. They affect the function of virtually every organ system. There are two biologically active thyroid hormones; T4 and T3. T4 is solely a product of the thyroid gland, whereas T3 is a product of the thyroid and of many other tissues, in which it is produced by de-iodination of T4. Iodine is essential for normal thyroid function. In Australia, about 16% of women have been found to have moderate to severe iodine deficiency. Thyroid hormone production is regulated by thyroid stimulating hormone (TSH). The secretion of TSH is inhibited by T4 and T3, and is stimulated by thyrotropin-releasing hormone (TRH). Nutritional, hormonal and illness-related factors regulate the extra-thyroid conversion of T4 to T3 and the effect of these factors differs in different tissues.

Pregnancy is a state of increased thyroid demand necessitating an increase in thyroid hormone synthesis by as much as 50% and therefore an increase in iodine requirements. The foetus is dependent on trans-placental transfer of maternal T4, especially during the first trimester of pregnancy. Maternal T3 does not cross the placenta. De-iodination of maternal T4 by the foetus results in local foetal production of T3, which is particularly important for neurological development.

Although the foetal thyroid gland starts forming earlier, functioning in the form of trapping and concentration of iodine and synthesis of T4 and T3 is only commences at 10-12 weeks. Control of thyroid function by the hypothalamo-pituitary axis is only established around 18 weeks (this continues maturing until 2 years of age). The foetal thyroid does not produce significant amounts of T4 until the second half of the pregnancy when levels rise steadily until term under the action of TSH. Serum TSH concentrations rise gradually from 12 weeks until term. The foetus is dependent on maternal iodine intake throughout pregnancy, and iodine is transferred across the placenta for foetal thyroid hormone production.

A number of conditions which may impact on neonatal thyroid status include:

- Gestational and postnatal age
- Non-thyroid illness, drugs
- Maternal hypothyroidism (untreated)
- Maternal iodine deficiency
- Maternal hyperthyroidism / presence of TSH-receptor Abs
- Congenital hypothyroidism.

Term Infants

The normal full term neonate shows a marked and rapid increase in serum TSH within 30 minutes of birth (60-80 mU/L). This decreases rapidly to about 20 mU/L at 24 hours and then more slowly to 6-10 mU/L at one week. The initial surge in TSH stimulates thyroidal T4 secretion, so that serum T4 and T3 concentration rise to peak at 24-36 hours of life. They gradually fall in the first four weeks of life, levelling off to just slightly above adult levels.

Preterm Infants

Thyroid function is related to both gestational and post-natal age. In general, preterm infants show the same changes at birth as term infants, but the changes are smaller in magnitude. This is most likely because of immaturity of the hypothalamic-pituitary axis. In babies > 30 weeks, T4 rises to peak at 1 week and then falls. The levels overlap with the normal range for a term newborn after the first week of life. In the more preterm infants (< 30 weeks), T4 falls in the first week of life before gradually rising to overlap the range of normal term infants by 3-6 weeks.
Preterm infants with respiratory distress syndrome and other medical problems tend not to have the expected postnatal increases in serum TSH, T4 and T3. Consequently, levels of these hormones may decrease at 24 hours and be low until the infant recovers or begins to gain weight. If these infants are treated with glucocorticoids or dopamine, these drugs may also decrease TSH secretion.

**Key Points**

- Thyroid Function Tests (TFTs) done immediately after birth can be difficult to interpret and must be related to the normal postnatal changes expected in thyroid function. Early measurement of TSH levels (< 48 hours) after birth may give a false positive elevation in TSH, which is seen normally immediately after delivery. Early measurement of TFT and/or TSH Rc Ab may be useful in identifying biochemical thyrotoxicosis in infants at risk, or in whom clinical suspicion is raised.

- A Newborn Screening Test (Guthrie) detects an elevated TSH in the neonate (therefore detecting only primary hypothyroidism). Perth Children’s Hospital (PCH) Endocrine Department is advised of abnormal results.

- Preterm infant TFT results should be interpreted with caution and with reliance on literature values. The immature hypothalamo-pituitary axis implies a delay in elevation of TSH in response to hypothyroidism that may only be detected with repeated screening after several weeks. Consultation with PCH endocrine department is advised.

- Treatment for neonatal hypothyroidism should be commenced as soon as possible as delay can result in irreversible neuro-cognitive damage.

- Neonatal thyrotoxicosis is a rare condition but can be life-threatening. It arises as a result of trans-placental passage of TSH receptor antibodies, usually in the presence of active maternal Graves' disease. Anti-thyroid (thionamide) medication and beta-blocker therapy should be considered in consultation with Endocrinology Dept. at PCH.

**Maternal Thyroid Disease**

**Maternal Hypothyroidism**

Untreated maternal hypothyroidism may cause obstetric complications such as miscarriage, premature birth, still birth, and low birth-weight as well as long term neuro-cognitive consequences for the neonate. It is still controversial whether there should be universal screening for maternal hypothyroidism or whether this should be done on a case-by-case basis. Preferably it should occur before a woman falls pregnant to prevent any damage occurring during the first trimester. If the maternal hypothyroidism is adequately treated with thyroxine (T4), there should be no impact on the neonate and the only testing necessary is the TSH screen as part of the Guthrie newborn screening test.

**Causes:**

- Hashimoto’s autoimmune thyroiditis:
  - Most common cause (developed countries).
  - Presents late childhood / early adulthood.
- Medically / surgically treated Graves’ disease:
  - Past history of hyperthyroidism.
  - Infant at high risk of neonatal thyroid dysfunction.
- Congenital Hypothyroidism:
Thyroid Disorder: Care of the Infant Born to Women with Thyroid Disorders

- Detected at both or early childhood.
- Dyshormonogenesis.
- Hypothalamic-pituitary disorder.
- Iodine deficiency:
  - Common in underdeveloped areas of the world.

**Hashimoto Thyroiditis**
Hashimoto autoimmune thyroiditis represents the most common cause of maternal hypothyroidism, with an incidence of 2.5%. The diagnosis of Hashimoto thyroiditis is established by a combination of clinical features, presence of serum antibodies against thyroid antigens (mainly to thyroperoxidase and thyroglobulin), and appearance on thyroid sonogram.

**Maternal Congenital Hypothyroidism**
In cases of maternal congenital hypothyroidism (e.g. Thyroid aplasia, ectopia), the mother will be on regular thyroid replacement. If the neonate inherits the condition (risk: 2-5%) the TSH level will be elevated in an attempt to stimulate the absent/deficient gland.

In most cases, women with a hypothalamic-pituitary disorder will have deficiencies of multiple pituitary hormones. Isolated deficiency of TSH is rare. Mutations in a number of transcription factors for pituitary hormones have been identified, including HESX1, LHX3, LHX4, PROP1 and PIT1. Although phenotypic variance may be seen in these mutations, hypothyroidism may be predictable as part of broader spectrum of pituitary dysfunction. Importantly, hypothyroidism arising from such disorders will not be identified by NST / Guthrie card, as TSH levels are low.

**Iodine Deficiency**
Iodine deficiency is the commonest cause of hypothyroidism in the developing world. Many countries potentially are at risk for deficient dietary intake of iodine, with supplementation to meet recommended daily intake in bread, salt and other foodstuffs. The World Health Organisation recommends a daily iodine intake of 150 μg/day, increasing to 200-250 μg/day during pregnancy and lactation.

**Maternal Hyperthyroidism (Graves’ Disease)**
Maternal hyperthyroidism is mainly caused by auto-immune Graves’ disease. Although Graves’ disease occurs in 0.2% of women, only 1-5% of infants born to these mothers have neonatal Graves’ disease. Neonatal Graves’ disease is caused by the trans-placental passage of TSH receptor stimulating antibodies (TSH Rc-Ab) with those mothers having the highest titres are most prone to their infants developing neonatal thyrotoxicosis. It is therefore recommended that all women with active Graves’ disease or a history of previously treated Graves’ disease have the TSH Rc-Ab titres checked at 28-32 weeks gestation. Babies born to mothers with Graves’ disease may be hyperthyroid or hypothyroid at birth depending on the balance of maternal stimulating or inhibitory antibodies and anti-thyroid drug effect. All babies born to hyperthyroid women need to have their thyroid function and TSH receptor antibody status checked at birth or shortly thereafter.
Neonatal Thyroid Disease

Congenital Hypothyroidism in the Newborn

The incidence of congenital hypothyroidism is estimated at 1:2500 to 1:4000 live births. In Western Australia, 8-12 new cases are identified each year. Early diagnosis is critical to prevent irreversible neuro-developmental abnormalities.

A Newborn Screening Test (Guthrie) is performed after the first 48 hours and before 5 days following birth and will detect increased TSH levels. The normal level of the TSH assay on days 2-5 is <13 mU/L. Infants with initial TSH screening results of 13-30 mU/L have a repeat card collected as the first step. Only those infants with a repeat TSH >8 mU/L are referred to PCH Endocrinology for follow-up. Infants with initial TSH screening results > 30mU/L are referred directly to PCH Endocrinology for immediate recall and assessment. Ten percent of infants with congenital hypothyroidism have TSH values in the range 20-40 mU/L. In premature infants, IUGR and LBW infants a second screen at 2-4 weeks postnatal age should be performed to rule out primary hypothyroidism with a delayed TSH rise. Congenital hypothyroidism is associated congenital heart disease (10% vs 3% risk in normal population), particularly pulmonary stenosis, ASD and VSD.

Clinical Signs of Hypothyroidism in the Neonate:

- Goitre
- Intrauterine growth restriction
- Prolonged jaundice
- Poor weight gain
- Bradycardia
- Temp instability
- Large fontanelles
- Constipation
- Umbilical hernia
- Oedema
- Microcephaly
- Poor feeding
- Inactivity, sleepy

NOTE: Pendred Syndrome; Congenital hypothyroidism and sensori-neural deafness arising from abnormal transport protein (pendrin) involved in iodine transport and cochlear function.

Causes of Hypothyroidism in the Neonate

Permanent causes:
- Dysgenesis (80-90%):
  - Ectopic (45-50%).
  - Athyrotic (35-40%).
- Dyshormonogenesis (10-20%) - includes Pendred Syndrome.
- Other (5%) - includes TSH receptor mutations.

Transient causes:
- Exposure to iodine antiseptics.
- Maternal antithyroid medication.
- Auto-immune thyroid disease.
- Iodine deficiency / excess (maternal diet).

Congenital Hyperthyroidism in the Newborn

Neonatal thyrotoxicosis may be associated with significant morbidity and mortality if unrecognised or inadequately treated.

Causes of neonatal thyrotoxicosis:
- Maternal Graves’ Disease:
  - Trans-placental TSH Rc Ab (Stimulatory).
• Maternal Hashimoto’s Thyroiditis:
  • Rarely produces stimulatory TSH Rc Ab antibodies.
• Activating mutation of the TSH Receptor:
  • Suspect if maternal Hx of thyrotoxicosis from birth.

Risk factors for thyrotoxicosis presenting in the newborn are:
• Maternal history of hyperthyroidism / Graves’ disease.
• Mother on anti-thyroid treatment at the time of delivery.
• High maternal TSH Rc Ab titres during pregnancy (28-32 weeks gestation).
• Fetal signs of thyrotoxicosis:
  • Advanced bone age (e.g. lower femoral epiphysis on foetal US).
  • Hydrops / tachycardia / arrhythmia.
  • IUGR / preterm.
  • Hyperkinesis.
  • Goitre.

Clinical Signs of Hyperthyroidism in the Neonate

| Tachycardia | Arrhythmia | Hydrops |
| Intrauterine growth restriction | Craniostenosis | Microcephaly |
| Jaundice | Diarrhoea | Sweating |
| Thrombocytopenia |

Management of the Neonate at Risk of Thyroid Dysfunction

Managing the Infant at Risk of Hypothyroidism

• Infant of a mother with auto-immune (Hashimoto) thyroiditis:
  • Trans-placental passage of (inhibitory) TSH Rc Ab may produce transient hypothyroidism in the newborn. Maternal TSH Rc Ab titres are useful if available. The identification of a normal titre indicates low risk for post-natal thyroid dysfunction and the Guthrie / Newborn Screening Card is sufficient. Some authors have suggested undertaking TSH / fT4 levels at 7-10 days if maternal titres are elevated or not available.

• Infant of a mother with hypothyroidism secondary to treated Graves’ disease:
  • Graves’ disease may be managed medically, by surgical resection or radio-iodine ablation. All treatments have the potential (or intention) to render the mother hypothyroid. Importantly, the mother may still be producing TSH Rc Ab’s and thus there is potential for neonatal thyrotoxicosis in the infant. TSH Rc Ab titres performed during the 3rd trimester is recommended in order to assess risk for neonatal thyrotoxicosis. Titres of 5 times the normal level have been considered as high risk for the development of neonatal thyrotoxicosis, although the possibility exists even for lower titres.

• Infant of a mother with congenital hypothyroidism:
  • Most frequently, the cause of congenital hypothyroidism in the mother is gland ectopia or agenesis. Less commonly, dyshormonogenes is may be the cause. In all such cases, hypothyroidism in the newborn will be detected by elevation of the TSH on Guthrie / NST. In the rare case of
hypothalamic-pituitary disorders, TSH levels will be low and will NOT be detected by the Guthrie / NST.

- In the case of suspected dyshormonogenesis, family history of thyroid dysfunction or Pendred syndrome, hearing testing should be performed. Sensori-neural deafness in Pendred syndrome is consequent to anatomical changes in the inner ear (Mondini malformation) and may deteriorate over time. The Australian Paediatric Endocrine Group suggests AABR or OAE testing at 4-8 weeks with three monthly testing for at least the first year in such cases.

**Treatment of Neonatal Hypothyroidism**

- **Neonatal hypothyroidism should be considered a medical emergency.** Early treatment with thyroxine is essential and can prevent significant neuro-cognitive damage. Babies with a positive Guthrie screen are notified to the Endocrine Department at PCH (automatically). After clinical assessment, a definitive TFT and antibody testing is performed. Treatment with thyroxine is commenced at 10-15 microgram/kg/day.
- The goal of therapy is to normalise T4 levels within 2 weeks, and TSH within 1 month.

**Managing the Infant at Risk of Hyperthyroidism/Thyrotoxicosis**

- Trans-placental transfer of TSH receptor stimulating antibodies from the serum of mothers with active, inactive or treated Graves’ disease is the usual cause of neonatal thyrotoxicosis. Diagnosis of neonatal hyperthyroidism should be confirmed by measurement of serum TSH, TSH Rc-Ab and FT4 levels, blood for which may be collected from cord blood.
- Suspected or confirmed neonatal hyperthyroidism / thyrotoxicosis should be referred to the Endocrinology consultant on-call for PCH after discussion with the Neonatologist / Senior Registrar on-call at KEMH.

**Treatment of Neonatal Hyperthyroidism / Thyrotoxicosis**

- Initiate anti-thyroid drugs promptly in consultation with Paediatric Endocrinologist
- FT4 levels guide therapeutic dose and duration.
- Propranolol may be indicated for persistent tachycardia.
- Digoxin and/or diuretic may be required for cardiac failure.
- Often treatment can be withdrawn in several weeks or months, once maternal antibodies (TSH Rc-Ab) have cleared. Cessation of treatment is determined by clinical findings and measurements of serum TSH and FT4.
- Medical management of biochemical or clinical thyrotoxicosis in the neonate is by way of the thionamides carbimazole and propylthiouracil (PTU). Both medications inhibit thyroid hormone synthesis by preventing organification of iodine and the coupling of iodothyronine residues. PTU also inhibits the de-iodination of T4 to T3 and as a result, smaller dose changes are often required. PTU is commenced at a dose of 2.5-5 mg/kg, 12 hourly. Carbimazole dose is 250 µg/kg, TDS. Importantly, a clinical response should not be expected until colloid stores are depleted. Adjunct treatments include iodine containing solutions (e.g. potassium iodide, Lugol’s solution), β-blockers,
diuretics/digoxin and prednisolone. Glucocorticoids suppress thyroid hormone release and decrease the de-iodination of T4 to T3. Treatment for Graves’ related hyper-stimulation is usually required for 4-8 weeks.

- **Education**: Advise parents:
  - Regular monitoring of T4 and TSH is required – normally through Endocrinology Dept, PCH.
  - Breastfeeding is not contraindicated if the mother is on small to moderate doses of anti-thyroid medications. However, neonatal TFTs are required.
  - There is risk of recurrence in future pregnancies.
  - Radioactive iodine is totally contra-indicated during breast-feeding.

**Breastfeeding Advice for Infants of Mothers with Thyroid Disease**

- **Maternal Hypothyroidism**
  - There is no contra-indication to breast-feeding for mothers requiring thyroxine.

- **Maternal Hyperthyroidism**
  - PTU and the active metabolite of carbimazole (methimazole) are both detectable in breast milk. The fractional protein binding of PTU is significantly higher than methimazole, and is thus secreted in breast milk at much lower concentration. Milk to serum ratio for PTU is 0.1, compared to ratio of 1 for methimazole. Neither medication is contra-indicated in breastfeeding.
  - Radio-iodine treatment is an absolute contra-indication to breastfeeding.

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**GP Referral Letter** for Neonate Managed for Maternal Thyroid Disorder
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