Neonatal Thyroid Disorders

INDEX

Introduction:

Thyroid hormones are essential for the normal development of the brain. Thyroid disorders in the newborn form a complex group of conditions, many of which are the focus of active research at present. Well established screening programmes have been implemented to detect **congenital hypothyroidism**, which is associated with mental and growth retardation if left undetected and untreated. Thyroid status in the newborn is also influenced by **maternal thyroid disease**, with maternal thyroid disease associated with adverse pregnancy outcomes including neonatal encephalopathy [1, 2], and infants of mothers with Graves disease at risk of neonatal thyrotoxicosis. **Iodine deficiency** impacts on many populations to result in transient neonatal hypothyroidism and goitre, with potentially negative effects on infant and child development [3, 4]. Iodine excess may result from use of iodine containing antiseptics to mother or infant, radiology contrast agents for line insertion and amiodorone in mother or infant. **Iodine excess** has been associated with transient hypothyroidism especially in preterm infants [5-7], although its longer term effects are unknown. **Transient hypothyroxinemia** in preterm infants has been reported to be associated with adverse developmental outcomes [8-12]. However, there is no consensus on definition of hypothyroxinemia, and trials of treatment of preterm infants at risk of transient hypothyroxinemia are yet to demonstrate a benefit [13-15]. As transient hypothyroxinemia is associated with illness severity in preterm infants [16], it may be that the association with abnormal developmental outcome is due to these factors and not the thyroid response. This guideline provides a pragmatic, evidence based approach to dealing with thyroid disorders in the newborn infant.

Congenital hypothyroidism

Deficiency of thyroid hormone may result in mental and growth retardation if congenital hypothyroidism is not diagnosed and treated adequately early in life [17, 18]. Most infants will still appear clinically normal before 3 months of age, by which time some brain damage has usually occurred. Symptoms or signs, when present, may include prolonged neonatal jaundice, constipation, lethargy and poor muscle tone, poor feeding, a large tongue, coarse facies, wide fontanelle, distended abdomen and umbilical hernia.

Definitions:

- Primary hypothyroidism: causes high TSH levels on newborn screen

- Secondary hypothyroidism: low TSH not detected on newborn screen. Usually associated with other pituitary hormone deficiencies. In the Netherlands population based report, the prevalence of central congenital hypothyroidism was 1 case per 16 404 live newborns (95% CI 1 case per 13 174 infants to 1 case per 21 173 infants) [19].

Incidence and risk factors: The incidence of primary congenital hypothyroidism was reported as 1:3,541 in Victoria between 1977-88 [20], and 1:2824 in Western Australia between 1988-98 [21]. Common causes of primary congenital hypothyroidism include [20]:

- Dysgenesis (various abnormalities in the formation of the thyroid gland).
    - Athyrosis (no gland) 33%
    - Ectopic thyroid (small displaced gland) 46%
    - Hemithyroid (only one half present) - uncommon
- Dyshormonogenesis (a hereditary inability to manufacture thyroid hormones due to various rare enzyme defects) 11%

Screening: The initial screening test in NSW is the TSH (Thyroid Stimulating Hormone) assay. When TSH is slightly increased an urgent repeat sample is requested by letter. When screening results are significantly abnormal the infant's physician is notified by telephone.

- Important history includes maternal diet, drugs or autoimmune disease.
- Examine for clinical features including coarse facial features, large tongue, umbilical hernia, constipation, poor feeding, intellectual and developmental delay, goitre, jaundice, growth parameters and other congenital problems (eg heart disease).

Screening considerations: There is a TSH surge in the first 24 to 36 hours of life. Screening before 48 hours produces a high rate of false positive results due to this surge. The results can also be affected by maternal thyroid antibodies, medication for maternal thyroid disease, maternal iodine deficiency, excessive dietary iodine and external application of iodine to mother or baby.

Diagnosis: For infants with a positive screen, an urgent blood sample should be collected to perform thyroid function tests:

- fT3, fT4, TSH

As well, further diagnostic studies are indicated:

- A thyroid scan (99mTc pertechnetate scan) thyroid scans are better at detecting ectopic thyroid tissue [19, 22]. However, treatment should not be delayed if a thyroid scan is not readily available. [Contact Nuclear Medicine CHW: Phone: 9845 2890; Fax: 9845 2892]
- Thyroid ultrasound is indicated if there is no uptake on the thyroid nuclear scan.- ultrasound is able to detect tissue not visualised on isotope scanning, and shows abnormalities of thyroid volume and morphology [22]. [Contact Medical imaging CHW: Phone: 9845 2944; Fax: 9845 2943]
- With a history of maternal autoimmune disease or a non-dysplastic thyroid on imaging, maternal and baby thyroid antibodies measurements are indicated.
- Bone age x-ray (knee), are used to determine the type, age of onset and severity of hypothyroidism.

Interventions:

- Contact the on call Endocrinologist at either Sydney Childrens Hospital (93821111) or Childrens Hospital Westmead (98450000)
- Commence thyroxine 10 μg/kg/ day as soon as diagnosis is confirmed. A meta-analysis of observations studies reported that higher starting doses result in more rapid normalisation of thyroid indices but effects on growth and development were uncertain. Concerns were expressed about the possibility of increased behavioral problems at 8 years [23]. In a randomised study, early treatment with more repid correction of thyroid function has been demonstrated in trials to produce better developmental outcomes [17, 18]. There does not appear to be any additional benefit from use of T3 treatment added to T4 [24].
- Repeat thyroid function tests at 12 weeks, 6 weeks, 3 months and thereafter 2 to 3 monthly until 3 years and then 4 to 6 monthly.

- Once TSH in normal range: continue with 100 micrograms/m2 daily titrated to fT4 and TSH. Note:

$$\text{Body Surface Area} \;=\; \frac{[\text{height (cm)} \times \text{weight (kg)}]}{3600}$$

- Treatment is aimed at keeping the free T4 concentration in the upper third of the normal range and TSH suppressed into the normal range [17, 18].
- If dyshormonogenesis is suspected, hearing tests should be performed regularly for at least the first year of life and development monitored.

Infants with Down Syndrome: Infants with Down Syndrome may be at increased risk of congenital hypothyroidism [25]. These infants also have a population shift in T4 values and TSH at all ages, suggestive of a thyroid insensitivity to thyrotropin [26, 27]. In addition, they are at increased risk of autoimmune thyroiditis and possibly Graves Disease [26, 28].

- In infants with Down Syndrome, daily thyroxine doses adjusted at regular intervals to maintain plasma TSH in its normal range and free T4 concentrations in its high-normal range, improved growth and development [29].

Infants with elevated TSH and normal T4: There is controversy regarding the need for thyroxine therapy in this setting. Apart from infants with Down Syndrome, there have been no long-term studies to evaluate the effect of thyroxine supplementation on cognitive development in this group of patients.

- Infants with TSH > 10 mIU/L: The AAP recommends that if TSH elevation persists, the infant should be treated [30]. If such infants are not treated, measurement of FT4 and TSH should be repeated in 2 and 4 weeks, and treatment should be initiated promptly if the FT4 and TSH concentrations have not normalized.
- Infants with TSH 6 to 10 mIU/L: The AAP does not currently recommend treatment of infants with TSH elevations between 6 and 10 mIU/L that persist after the first month of life. However, if a decision is made to treat such children, a trial off therapy at 3 years of age is recommended.

Transient hypothyroidism

Incidence and risk factors: Transient congenital hypothyroidism is diagnosed by high TSH levels and low free T4 levels soon after birth but with spontaneous resolution over time.[31] In an Italian study, 50% was attributed to maternal and/or neonatal iodine exposure and a third from passive transfer of maternal antibodies [32]. The major causes of transient congenital hypothyroidism are:

- Iodine deficiency,
- Iodine excess, and
- Passive transfer of maternal thyrotropin receptor blocking antibodies.

Iodine deficiency: Iodine is an essential element for the production of thyroid hormones. Iodine requirements increase during pregnancy. The urinary iodine concentration (UIC) is considered a good indicator of a previous days dietary iodine intake, as over 90% of iodine absorbed is eventually excreted in the urine [33]. Globally, more than 1.9 billion individuals have inadequate iodine nutrition (defined as urinary iodine excretion <100 μg/L).[34, 35]

Incidence and risk factors: The newborn thyroid has limited iodine stores, and even mild deficiency will increase TSH secretion. In epidemiological studies, populations with 3% of newborns with TSH levels > 5 mIU/L whole-blood are considered at risk of iodine deficiency. In a recent NSW cohort of pregnant women and their infants, the median UIC for pregnant women was 85 μg/L, indicating mild iodine deficiency. Almost 17% of pregnant women had a UIC < 50 μg/L, and 2.2% of newborns had TSH values >

5 mIU/L. Mothers with a UIC < 50 µg/L were 2.6 times more likely to have a baby with a TSH level > 5mIU/L.[36] The incidence of iodine deficiency in Australian newborns requires further study. A survey of Australian children aged 8-10 years found the national median urinary iodine excretion was 104 µg/L, representing borderline iodine status, with NSW children being mildly iodine deficient with median urinary iodine levels 89 µg/L [37].

Consequences:
Iodine deficiency can lead to congenital hypothyroidism and irreversible mental retardation, making it the most common preventable cause of mental retardation [38, 39]. There is also concern that mild and subclinical iodine deficiency can lead to neuropsychomotor deficits.[40, 41] A 2005 meta-analysis of 37 studies in Chinese publications, which included 12 291 children younger than 16 years, concluded that IQs averaged 125 points lower for children growing up in iodine deficient areas than in sufficient areas [41]. In addition, iodine deficiency in a population results in a high recall rate in neonatal screening programs for congenital hypothyroidism based on an elevated TSH [42, 43] and increased prevalence of goiter.[35, 44] Concern has been expressed that low iodine intake may result in depressed thyroid hormone levels seen in preterm infants (see section on transient hypothyroxinemia).[45] Trials have suggested that iodine supplementation in children results in iodine decreasing goitre rates and improved iodine status, with positive effects on physical and mental development [41] and mortality also reported.[46]

Interventions:

- **For populations:** salt iodization is the recommended strategy for iodine deficiency disorders control.[35, 47] WHO recommends adequate iodine intake to achieve a urinary iodine concentration of 100200 µg/l/day.[48]
- **Pregnant women:** A meta-analysis of observational studies reported that children who received iodine supplementation prenatally and postnatally averaged 87 points higher than those who did not [41]. Iodine supplementation in the first and second trimesters of pregnancy decreased the prevalence of moderate and severe neurological abnormalities and increased developmental test scores through 7 years, compared with supplementation later in pregnancy or treatment after birth. Currently, studies are required to determine the iodine intake and status of pregnant women in Australia.
- **Children:** Systematic review [46] of trials of iodine in children found iodine supplementation (especially iodised oil) is an effective means of decreasing goitre rates and improving iodine status in children. Indications of positive effects on physical and mental development and mortality were also reported.
- **Newborn infants:** The immediate neonatal requirements for iodine are high as a result of the postnatal thyroid hormone surge and the small calculated intra-thyroidal reserve pool of thyroid hormone. The recommended enteral intake of iodine for is at least 15 µg/kg/day for term infants and 30 µg/kg/day for preterm infants.[3] The iodine intake of newborns is entirely dependent on the iodine content of breast milk and the formula preparations used to feed them, and/or the parenteral nutrition supply [3]. In turn, the iodine content of breast milk is dependent on the iodine status of the lactating woman and reduced by maternal smoking [49].
- **Preterm infants:** Only one randomised trial has examined the effect of iodine supplementation in preterm infants. Infants (n=121) were randomised to standard (68 µg/l) versus increased (272 µg/l) iodine in preterm formula. There was no effect on thyroid hormone levels and no effect on growth or neonatal morbidity. Neurodevelopment was not reported.[50]

Future research: The iodine status of infants and the effects of iodine supplementation of iodine deficient infants need further study. A trial (I2S2 trial - http://www.euthyroid.org/) is proposed to study the effects of supplementation of parenterally fed infants with potassium iodide 30 µg/kg/day or placebo started within 42 hrs of birth for 28 days.

....

Iodine excess:
Infants exposed to excess iodine are at risk of iodine overload resulting in transient hypothyroidism. The long term effects of iodine excess and transient neonatal hypothyroidism are unknown.

Incidence and risk factors: The incidence of transient hypothyroidism related to iodine overload depends upon the cumulative exposure to iodine of the newborn infant, with one Australian study reporting

an incidence of 25% in an iodine using perinatal centre, compared to none in a control centre not using iodine containing antiseptics or contast agents.[5] Preterm and low birth weight infants appear to be at greater risk than term infants.[5-7] The data suggest that repeated cumulative exposure, both antenatally and postnatally, place the infant at high risk from iodine excess and transient hypothyroidism. Risk factors for neonatal iodine overload include:

- Maternal exposure to iodine
  - povidone-iodine use for skin disinfectant during caesarean section or vaginal delivery [43] and
  - amiodorone treatment of maternal, fetal arrhythmia or neonatal [51, 52].
- Postnatal exposure to iodine during:
  - routine umbilical cord care and skin disinfection prior to procedures,[5, 53] and
  - injection of iodinated contrast material for radiographic visualization of central venous lines.[6, 7]
  - One study in 50 term and preterm infants reported no effect on thyroid function from a single exposure to povidone-iodine antisepsis with only a slight elevation in urinary iodine excretion [54].

A study is planned in the UK (I2X2 study - http://www.euthyroid.org/) to determine the incidence of transient hypothyroidism following exposure to iodine in infants less than 32 weeks gestation.

Consequences: There are no published reports on the effect of transient hypothyroidism due to iodine overload on neonatal morbidity, mortality and subsequent neurodevelopment.

Interventions: There are no data from controlled trials to determine whether thyroid hormone treatment of infants with transient hypothyroidism affect neurodevelopmental outcome. In a cohort study with incomplete ascertainment of thyroid status and neurodevelopmental outcome, there was no difference in the development or intelligence scores between infants who had transient hypothyroidism (TSH >20 iU/L) and those with normal TSH levels. The incidence of neurodevelopmental disability did not differ between infants with and without transient hypothyroidism. Infants with transient hypothyroidism were treated with thyroid hormone replacement.[55]

Antisepsis: Systematic review [56] of trials of chlorhexidine versus povidone-iodine for skin and catheter antisepsis report reduced sepsis rates in infants treated with chlorhexidine (RR of catheter-related bloodstream infection 0.49 (95% CI: 0.28, 0.88)). Trials typically used chlorhexidine concentrations >0.5% or chlorhexidine in 70% alcohol. In neonatal units using povidone-iodine, trials of chlorhexidine versus povidone-iodine are required. In developed countries, there is no evidence that use of an antiseptic (including povidone-iodine) for cord care is better than keeping the cord clean and dry without antisepsis use [57]. In a developing setting, a cluster randomised trial of 4% chlorhexidine for cord care versus dry cord care, severe oomphalitis was reduced by 75% (RR 0.25, 95% CI 0.12-0.53) and neonatal mortality was 24% lower (RR 0.76, 95% CI 0.55-1.04). [58] Povidone-iodine is not used in RPA Newborn Care.

Radiology contrast agents: There are reports [6, 7] of transient hypothyroidism in response to iodinated contrast agents, although not all are consistent. All agents have iodine but at differing concentrations liberating differing quantities of free iodine. In view of concerns regarding the potential for iodine overload, the use of radio-opaque contrast materials should be limited to central line placements which are inadequately visualized by plain x-ray and ultrasound. Plain x-ray has been reported to be imprecise in determining central line tip position in neonates [59-61].

Transient hypothyroxinemia of prematurity

In preterm infants, levels of T4 and fT4 in the first day vary directly with gestation.[12, 62] However, unlike term infants, the concentrations of T4 and fT4 decrease to reach a nadir between day 10 and 14 after birth that is more severe at lower gestations and birth weights.[62, 63] Thyroid hormone levels then tend to return to normal levels after three weeks, but continue to increase up to six to eight weeks after birth.[64] Furthermore, the levels of T4 and fT4 in premature infants are lower than those seen in the normal fetus at similar gestational ages [65-67].

This period of low thyroid hormone levels in infants born prematurely has been termed "transient hypothyroxinemia of prematurity" (low T4, normal thyrotropin [TSH]).

Incidence and risk factors: There is no consistent definition of transient hypothyroxinemia in newborn infants. Studies have reported:

- Incidence of infants with severely depressed T4 values (below 4 mg/dL) ranged from 40% at 23 weeks gestation to 10.2% at 28 weeks gestation.[68]
- In surviving VLBW infants, 1.5% had screening T4 concentrations that were immeasurably low (<3.9 nmol/L = 0.3 µg/dl) [63].
- Incidence of day 7 T4 levels >2 SD below adjusted T4 cord level of equivalent gestational age, 14% of 23-27 week gestation, 1% of 28-30 week and 3% of the 31-34 week were hypothyroxinaemic.[69]

Risk factors (associations) for transient hypothyroxinemia reported in observational studies include:

- Lower gestational age [31, 70-74]
- Maternal pre-eclampsia with placental insufficiency [75],
- Fetal growth restriction [76],
- Perinatal asphyxia [77],
- Respiratory distress syndrome [70, 76],
- More severe respiratory disease [71],
- Mechanical ventilation [31, 71],
- Low diastolic blood pressure [71] and
- Dopamine infusions [31, 74], and
- Multiple factors including bacteremia, endotracheal bacterial cultures, persistent ductus arteriosus, necrotizing enterocolitis, cerebral ultrasonography changes, oxygen dependence at 28 d, and the use of aminophylline, caffeine, dexamethasone, diamorphine, and dopamine [78].

Consequences: Infants who are extremely premature and sick are more likely to have transient hypothyroxinemia. Whether transient hypothyroxinemia is causative of adverse neonatal outcomes or is merely associated with illness severity is unclear. Associations with transient hypothyroxinemia reported in observational studies include:

- Intraventricular haemorrhage, [73, 79]
- Chronic lung disease, [71]
- Death, [71, 73, 80] and
- Neurodevelopmental disability: Three cohort studies [8-12] have documented an association between low thyroid hormone levels (T3 or T4) in the first weeks after birth and abnormal neurodevelopmental outcome. All three cohorts documented a measure of abnormal mental development in children who had low neonatal thyroid hormone levels. The associations in the cohorts persisted despite correction for potential confounders including gestation, measures of fetal growth (either birth weight or presence of growth restriction) and, in some studies, many factors relating to severity of illness in preterm infants and independent risk factors for abnormal neurodevelopmental outcome. The studies reported:
    - A 4.4 fold increase in risk of disabling cerebral palsy and a 7 point reduction in mental development index at 2 years [12], and an increased risk of school failure at 9 years [8] in infants with a T4 level in the 1st week >3 SD below the normal values (<60nmol/L),
    - A 8.3 and 7.4 point disadvantages in Bayley mental and motor scales and a 8.6 point disadvantage on the academic scale of Developmental Profile II at 18 months' corrected age in infants with a T3 level <0.3 nmol/L,[10]
    - An association between low T4 levels and failure to meet developmental milestones at 2 years.[11]

Interventions: Trials of thyroid hormones in preterm infants have not demonstrated any benefit from use of thyroid hormones for prevention of neonatal morbidity or long term neurodevelopmental impairment. The following reviews the evidence from systematic reviews of thyroid hormones in preterm infants:

- Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants: systematic review [13] found 4 trials enrolling 318 infants. All studies commenced treatment in the first 48 hours, with doses of T4 ranging from 8 to 20 µg/kg/day. No significant difference was found in neonatal morbidity, mortality or neurodevelopmental outcome up to 10 years in infants who received thyroid hormones compared to control. A subgroup analysis from one trial [81] of infants born <27 weeks gestation reporting a benefit from thyroid hormones should be viewed with caution

given imbalances after randomisation and the fact the analysis was not prespecified.

- Postnatal thyroid hormones for preterm infants with transient hypothyroxinemia: systematic review [15] found one trial enrolling 23 infants <1250 g and 25 - 28 weeks gestation with transient hypothyroxinemia (serum total T4 =4 µg/dl and TSH =20 iU/L) randomised to thyroxine 10 µg/kg/day or placebo beginning day 15 and continuing for seven weeks. No significant difference was reported any neonatal morbidity up to 36 weeks corrected age and no difference in growth in weight, head circumference or length. Neurodevelopmental follow up was inadequate to draw any conclusions from.
- Postnatal thyroid hormones for respiratory distress syndrome in preterm infants: systematic review [14] found 2 studies that enrolled preterm infants with respiratory distress, with one study comparing treatment with L-thyroxine 50 µg/dose at 1 and 24 hours to no treatment, and the other L-triiodothyronine 50 µg/day in two divided doses for two days or no treatment. Neither study reported any significant benefits in neonatal morbidity or mortality from use of thyroid hormones.

Infants of mothers with Hashimotos thyroiditis

Infants of mothers with Hashimotos thyroiditis are at low risk of transient hypothyroidism from thyroid blocking antibodies (incidence estimated at 1:180000), and rarely of thyrotoxicosis from coexistent thyroid stimulating antibodies. Most infants with transient hypothyroidism born to mothers with Hashimotos thyroiditis are identified by routine neonatal thyroid TSH screening.[82] There is conflicting advice on whether it is necessary to perform additional thyroid function tests on infants of mothers with Hashimotos thyroiditis [82, 83]. Until evidence is presented to the contrary, infants of mothers with Hashimotos thyroiditis should have the routine NSW Newborn Screening Programme TSH measurement on day 3 or 4.

Infants of mothers with Graves Disease

Neonatal thyrotoxicosis is rare condition caused by the transplacental passage of thyroid stimulating immunoglobulins (TSI) from mothers with Graves disease or, more rarely, Hashimotos thyroiditis. TSIs may continue to be produced even after ablation of the thyroid gland with surgery or radioiodine. Neonatal thyrotoxicosis secondary to TSIs is a transient disorder, limited by the clearance of maternal antibody from the babys circulation. Rarely, thyrotoxicosis may be due to inherited activating mutations in the TSH receptor.

Incidence and risk factors: The reported prevalence of Graves disease in pregnant women is approximately 0.2%. Although it is usually stated that only 11.5% of their offspring will have overt hyperthyroidism, higher incidences have been reported (5%-12.5%). A further 3% of babies of mothers with Graves disease have biochemical thyrotoxicosis in the absence of symptoms.[83]

Consequences: Fetal thyroid tissue function is established by 12 week gestation and by 25 week is almost functionally mature.

Effects on pregnancy: Although data are sparse, pregnancies affected by maternal hyperthyroidism may be at increased risk of:

- Miscarriage [84]
- Stillbirth [85]
- Intrauterine growth restriction [86]
- Preterm labor and other pregnancy complications including pregnancy induced hypertension and thyroid crisis [86]

Fetal effects: the fetus may develop goitre, tachycardia, hydrops associated with heart failure, growth retardation, craniosynostosis, increased foetal motility and accelerated bone maturation.

Neonatal effects: In the neonate, overt symptoms and signs usually occur in the first few days of life and may last for 36 months, proportional to the clearance of maternal IgG [87]. However, overt thyrotoxicosis has been reported to occur as late as 45 days [87], delayed by the presence of transplacentally transferred maternal antithyroid drugs or blocking antibodies. Affected neonates may have

irritability, restlessness, goitre, excessive weight loss, failure to regain birth weight, diarrhoea, sweating, flushing and eye signs including peri-orbital edema, lid retraction and proptosis [86, 88-90]. Initial sinus tachycardia can progress to tachyarrhythmia and congestive cardiac failure [91]. Systemic [92] and pulmonary hypertension may be present [93, 94]. Neonatal thyrotoxicosis is reported to have a mortality of 1625% [89, 95]. Most infants have a goitre. Advanced bone age, craniosynostosis, and microcephaly may be evident in both the fetus and newborn.

Symptoms and signs of neonatal thyrotoxicosis:

- Restlessness
- Tachycardia
- Poor feeding and occasionally extreme hunger
- Excessive weight loss
- Diarrhoea

Long term outcome: Neonatal Graves' disease tends to resolve spontaneously within 3-12 weeks as maternal thyroid stimulating immunoglobulins are cleared from the circulation but subsequent development may be impaired although data are sparse. The developmental outcome for infants of mothers with treated hyperthyroidism is generally within the normal range and similar to a matched control group [96].

Screening: Infants at risk of congenital hyperthyroidism (Maternal Graves disease, family history of activating mutations in TSH receptor) should have the following screening:

Cord blood: fT4, fT3 and TSH

Age 2-7 days (with NBS): fT4, fT3 and TSH

Day 10-14: fT4, fT3 and TSH if mother on antithyroid medication

Note that infants of mothers on antithyroid medication or with coexistent blocking antibodies may have delayed onset of signs and may need additional screening.

Prevention: Infants of mothers with Graves disease during pregnancy who are appropriately managed with antithyroid medication will usually have infants who are asymptomatic, although they are still at risk of biochemical hyperthyroidism (T4 >35 pmol/L). [97]

If hyperthyroid:

1. Contact the on call Endocrinologist at either Sydney Childrens Hospital (93821111) or Childrens Hospital Westmead (98450000)

2. The treatment of thyrotoxicosis is supported by case reports in the literature and is consistent with the treatment of hyperthyroidism in other populations of patients. Thyrotoxicosis in the newborn may be treated with either:

   - **Propylthiouracil (PTU)**: 510 mg/kg/day in three divided doses. PTU inhibits the synthesis of thyroid hormones by blocking the oxidation of iodine in the thyroid gland and synthesis of thyroxine and triiodothyronine. Peak concentration occurs within 1 hour of ingestion. The major drug interaction is the enhancement of anticoagulant activity.

     Or

   - **Carbimazole:** 0.51.5 mg/kg/day as a single daily dose:

     As the drugs block the synthesis but not the release of thyroid hormones, a clinical response to thionamides may not occur until the thyroid hormone stored in the colloid is depleted. Therefore

3. Iodide solution, which suppresses thyroid hormone synthesis and has a prompt effect in inhibiting the release of thyroid hormones, may be used in conjunction with case reports in the literature of their use. Either:

- o Saturated potassium iodide (KI) (48 mg iodine per drop) given in a dose of 1 drop daily, or
- o Lugols solution (5% KI; about 8mg iodine/drop) in a dose of 1 to 3 drops daily
4. Beta-Blockers are effective in controlling symptoms caused by adrenergic stimulation, in particular, cardiovascular symptoms associated with tachycardia or tachyarrhythmia. In addition, they inhibit deiodination of T4 to T3. Use:
   - o Propranolol 0.270.75 mg/kg 8 hourly. This may be administered orally or slow intravenous injection (over 10 minutes). The goal of therapy is reduction in heart rate to safe levels (<180bpm). Potential side effects include hypoglycaemia, bradycardia, and hypotension, so babies require close monitoring.
5. Specific treatment for cardiac failure may be required, for example
   - o Digoxin and
   - o Diuretics.
6. Severely thyrotoxic babies may be treated with prednisolone [98] which suppresses deiodination of T4 to T3 and compensates for hypercatabolism of endogenous glucocorticoids induced by T3 and T4. The dose of prednisolone is 2mg/kg/day.
7. Other general measures:
   - o Sedatives may also be helpful in managing irritability and restlessness.
   - o Monitor for hyperthermia and aim to achieve a neutral thermal environment.
   - o Assess fluid balance infants may have increased fluid requirements secondary to increased transepidermal water losses associated with hyperthermia and losses associated with diarrhoea.
   - o Assess growth infants may need increased caloric intake to ensure normal growth.

Breast feeding and maternal antithyroid drugs: It is important to monitor the thyroid function of infants who have perinatal exposure to antithyroid drugs.

Propylthiouracil: propylthiouracil crosses into the milk only in small amounts [99] and the thyroid function of infants of mothers on propylthiouracil normalized after birth whilst still breast feeding [100]. Mothers with Graves disease who are receiving propylthiouracil may be advised that breast-feeding their infants is safe.

Methimazole: methimazole is transferred into breast milk extremely well. However, normal thyroid function [101-103], developmental and intellectual outcomes have been reported in infants exposed to methimazole during pregnancy and breast feeding [104, 105].

Key Points

Key Point	Rating
Iodine deficiency may be associated with transient neonatal hypothyroidism, cretinism and mental retardation. WHO recommends adequate maternal iodine intake to achieve a urinary iodine concentration of 100200 µg/l/day	1a
All infants should be screened for congenital hypothyroidism on day 3-4 by heel prick test (TSH assay)	1a
Infants with clinical signs of hypothyroidism should have thyroid function tests performed (TSH, fT4 +/- fT3)	5
Infants with raised TSH on newborn screen should have confirmatory urgent blood sample for fT3, fT4, TSH. If confirmed: • Arrange urgent iodine scan and ultrasound • Commence thyroxine 10 µg/kg/day • Target fT4 high normal and TSH in normal range • Once fT4 and TSH in target range: give thyroxine 100µg/m2/day	1a
In preterm infants at risk of transient hypothyroxinemia thyroid hormone replacement has not been reported to improve neonatal morbidity, mortality or neurodevelopmental outcome	1a
In preterm infants, transient hypothyroidism from iodine excess has been reported from use	

of topical antiseptics containing iodine. The long term effects of transient hypothyroidism and treatment of transient hypothyroidism are unknown	1a
Infants of mothers with Graves Disease should have: • fT4, fT3 and TSH on cord blood, • day 2-7 (with NBS) and • additionally on day 14 if the mother is on antithyroid medications	2b
11.5% of the infants of mothers with Graves disease have overt hyperthyroidism, a further 3% have biochemical thyrotoxicosis in the absence of symptoms. All infants born to mothers with Graves Disease should be assessed for clinical signs: • irritability, restlessness, goitre, excessive weight loss, failure to regain birth weight, diarrhoea, sweating, flushing and eye signs including peri-orbital edema, lid retraction and proptosis, and sinus tachycardia.	2b

References

1. Sutton L, Sayer GP, Bajuk B, Richardson V, Berry G, Henderson-Smart DJ. Do very sick neonates born at term have antenatal risks? 1. Infants ventilated primarily for problems of adaptation to extra-uterine life. Acta Obstetricia et Gynecologica Scandinavica. 2001; 80: 905-16.

2. Badawi N, Kurinczuk JJ, Mackenzie CL, Keogh JM, Burton PR, Pemberton PJ, Stanley FJ. Maternal thyroid disease: A risk factor for newborn encephalopathy in term infants.[see comment]. BJOG: An International Journal of Obstetrics & Gynaecology. 2000; 107: 798-801.

3. Ares S, Quero J, Morreale de Escobar G. Neonatal iodine deficiency: Clinical aspects. Journal of Pediatric Endocrinology. 2005; 18 Suppl 1: 1257-64.

4. Delange F. Epidemiology and impact of iodine deficiency in pediatrics. Journal of Pediatric Endocrinology. 2005; 18 Suppl 1: 1245-51.

5. Smerdely P, Lim A, Boyages SC, Waite K, Wu D, Roberts V, Leslie G, Arnold J, John E, Eastman CJ. Topical iodine-containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. Lancet. 1989; 2: 661-4.

6. l'Allemand D, Gruters A, Beyer P, Weber B. Iodine in contrast agents and skin disinfectants is the major cause for hypothyroidism in premature infants during intensive care. Hormone Research. 1987; 28: 42-9.

7. Ares S, Pastor I, Quero J, Morreale de Escobar G. Thyroid complications, including overt hypothyroidism, related to the use of non-radiopaque silastic catheters for parenteral feeding in prematures requiring injection of small amounts of an iodinated contrast medium. Acta Paediatrica. 1995; 84: 579-81.

8. Den Ouden AL, Kok JH, Verkerk PH, Brand R, Verloove-Vanhorick SP. The relation between neonatal thyroxine levels and neurodevelopmental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. Pediatric Research. 1996; 39: 142-5.

9. Lucas A, Morley R, Fewtrell MS. Low triiodothyronine concentration in preterm infants and subsequent intelligence quotient (iq) at 8 year follow up. BMJ. 1996; 312: 1132-3; discussion 3-4.

10. Lucas A, Rennie J, Baker BA, Morley R. Low plasma triiodothyronine concentrations and outcome in preterm infants. Archives of Disease in Childhood. 1988; 63: 1201-6.

11. Meijer WJ, Verloove-Vanhorick SP, Brand R, van den Brande JL. Transient hypothyroxinaemia associated with developmental delay in very preterm infants. Archives of Disease in Childhood. 1992; 67: 944-7.

12. Reuss ML, Paneth N, Pinto-Martin JA, Lorenz JM, Susser M. The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age.[see comment]. New England Journal of

Medicine. 1996; 334: 821-7.

13. Osborn DA, Hunt RW. Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews. 2007: CD005948.

14. Osborn DA, Hunt RW. Postnatal thyroid hormones for respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews. 2007: CD005946.

15. Osborn DA, Hunt RW. Postnatal thyroid hormones for preterm infants with transient hypothyroxinaemia. Cochrane Database of Systematic Reviews. 2007: CD005945.

16. Paneth N. Does transient hypothyroxinemia cause abnormal neurodevelopment in premature infants? Clinics in Perinatology. 1998; 25: 627-43.

17. Selva KA, Harper A, Downs A, Blasco PA, Lafranchi SH. Neurodevelopmental outcomes in congenital hypothyroidism: Comparison of initial t4 dose and time to reach target t4 and tsh. Journal of Pediatrics. 2005; 147: 775-80.

18. Selva KA, Mandel SH, Rien L, Sesser D, Miyahira R, Skeels M, Nelson JC, Lafranchi SH. Initial treatment dose of l-thyroxine in congenital hypothyroidism.[see comment]. Journal of Pediatrics. 2002; 141: 786-92.

19. Lanting CI, van Tijn DA, Loeber JG, Vulsma T, de Vijlder JJ, Verkerk PH. Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program. Pediatrics. 2005; 116: 168-73.

20. Connelly JF, Coakley JC, Gold H, Francis I, Mathur KS, Rickards AL, Price GJ, Halliday JL, Wolfe R. Newborn screening for congenital hypothyroidism, victoria, australia, 1977-1997. Part 1: The screening programme, demography, baseline perinatal data and diagnostic classification. Journal of Pediatric Endocrinology. 2001; 14: 1597-610.

21. Kurinczuk JJ, Bower C, Lewis B, Byrne G. Congenital hypothyroidism in western australia 1981-1998. Journal of Paediatrics & Child Health. 2002; 38: 187-91.

22. Perry RJ, Maroo S, Maclennan AC, Jones JH, Donaldson MD. Combined ultrasound and isotope scanning is more informative in the diagnosis of congenital hypothyroidism than single scanning. Archives of Disease in Childhood. 2006; 91: 972-6.

23. Hrytsiuk I, Gilbert R, Logan S, Pindoria S, Brook CG. Starting dose of levothyroxine for the treatment of congenital hypothyroidism: A systematic review. Archives of Pediatrics & Adolescent Medicine. 2002; 156: 485-91.

24. Cassio A, Cacciari E, Cicognani A, Damiani G, Missiroli G, Corbelli E, Balsamo A, Bal M, Gualandi S. Treatment for congenital hypothyroidism: Thyroxine alone or thyroxine plus triiodothyronine? Pediatrics. 2003; 111: 1055-60.

25. Fort P, Lifshitz F, Bellisario R, Davis J, Lanes R, Pugliese M, Richman R, Post EM, David R. Abnormalities of thyroid function in infants with down syndrome. Journal of Pediatrics. 1984; 104: 545-9.

26. van Trotsenburg AS, Kempers MJ, Endert E, Tijssen JG, de Vijlder JJ, Vulsma T. Trisomy 21 causes persistent congenital hypothyroidism presumably of thyroidal origin. Thyroid. 2006; 16: 671-80.

27. van Trotsenburg AS, Vulsma T, van Santen HM, Cheung W, de Vijlder JJ. Lower neonatal screening thyroxine concentrations in down syndrome newborns. Journal of Clinical Endocrinology & Metabolism. 2003; 88: 1512-5.

28. Zori RT, Schatz DA, Ostrer H, Williams CA, Spillar R, Riley WJ. Relationship of autoimmunity to thyroid dysfunction in children and adults with down syndrome. American Journal of Medical Genetics - Supplement. 1990; 7: 238-41.

29. van Trotsenburg AS, Vulsma T, van Rozenburg-Marres SL, van Baar AL, Ridder JC, Heymans HS, Tijssen JG, de Vijlder JJ. The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old down syndrome children: A randomized clinical trial. Journal of Clinical

Endocrinology & Metabolism. 2005; 90: 3304-11.

30. American Academy of P, Rose SR, Section on Endocrinology and Committee on Genetics ATA, Brown RS, Public Health Committee LWPES, Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, Varma SK. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006; 117: 2290-303.

31. Kantor Herring MJ, Leef KH, Locke RG, Stefano JL, Bartoshesky L, Paul DA. Are perinatal risk factors helpful in predicting and optimizing treatment strategies for transient hypothyroxinemia in very-low-birth-weight infants? American Journal of Perinatology. 2003; 20: 333-9.

32. Weber G, Vigone MC, Rapa A, Bona G, Chiumello G. Neonatal transient hypothyroidism: Aetiological study. Italian collaborative study on transient hypothyroidism. Arch Dis Child Fetal Neonatal Ed. 1998; 79: F70-2.

33. International council for control of iodine deficiency disorders. Indicators for assessing idd status. IDD Newsletter. 1999; 15: 33-8.

34. Andersson M, Takkouche B, Egli I, Allen HE, de Benoist B. Current global iodine status and progress over the last decade towards the elimination of iodine deficiency. Bulletin of the World Health Organization. 2005; 83: 518-25.

35. de Benoist B, Andersson M, Takkouche B, Egli I. Prevalence of iodine deficiency worldwide.[see comment][comment]. Lancet. 2003; 362: 1859-60.

36. Travers CA, Guttikonda K, Norton CA, Lewis PR, Mollart LJ, Wiley V, Wilcken B, Eastman CJ, Boyages SC. Iodine status in pregnant women and their newborns: Are our babies at risk of iodine deficiency? Medical Journal of Australia. 2006; 184: 617-20.

37. Li M, Eastman CJ, Waite KV, Ma G, Zacharin MR, Topliss DJ, Harding PE, Walsh JP, Ward LC, Mortimer RH, Mackenzie EJ, Byth K, Doyle Z. Are australian children iodine deficient? Results of the australian national iodine nutrition study. Medical Journal of Australia. 2006; 184: 165-9.

38. Pharoah PO, Connolly KJ. Iodine and brain development.[see comment]. Developmental Medicine & Child Neurology. 1995; 37: 744-8.

39. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, Carter JA, International Child Development Steering G. Child development: Risk factors for adverse outcomes in developing countries. Lancet. 2007; 369: 145-57.

40. Lazarus JH. Thyroid hormone and intellectual development: A clinician's view. Thyroid. 1999; 9: 659-60.

41. Qian M, Wang D, Watkins WE, Gebski V, Yan YQ, Li M, Chen ZP. The effects of iodine on intelligence in children: A meta-analysis of studies conducted in china. Asia Pacific Journal of Clinical Nutrition. 2005; 14: 32-42.

42. Tylek-Lemaska D, Rybakowa M, Kumorowicz-Kopiec M, Dziatkowiak H, Ratajczak R. Iodine deficiency disorders incidence in neonates based on the experience with mass screening for congenital hypothyroidism in southeast poland in the years 1985-2000. Journal of Endocrinological Investigation. 2003; 26: 32-8.

43. McElduff A, McElduff P, Wiley V, Wilcken B. Neonatal thyrotropin as measured in a congenital hypothyroidism screening program: Influence of the mode of delivery. Journal of Clinical Endocrinology & Metabolism. 2005; 90: 6361-3.

44. Laurberg P, Jorgensen T, Perrild H, Ovesen L, Knudsen N, Pedersen IB, Rasmussen LB, Carle A, Vejbjerg P. The danish investigation on iodine intake and thyroid disease, danthyr: Status and perspectives.[erratum appears in eur j endocrinol. 2006 oct;155(4):643]. European Journal of Endocrinology. 2006; 155: 219-28.

45. Ares S, Escobar-Morreale HF, Quero J, Duran S, Presas MJ, Herruzo R, Morreale de Escobar G. Neonatal hypothyroxinemia: Effects of iodine intake and premature birth.[see comment]. Journal of Clinical Endocrinology & Metabolism. 1997; 82: 1704-12.

46. Angermayr L, Clar C. Iodine supplementation for preventing iodine deficiency disorders in children. Cochrane Database of Systematic Reviews. 2004: CD003819.

47. Wu T, Liu GJ, Li P, Clar C. Iodised salt for preventing iodine deficiency disorders. Cochrane Database of Systematic Reviews. 2002: CD003204.

48. WHO. The safe use of iodised oil during pregnancy. Bull WHO. 1996; 74: 1-3.

49. Laurberg P, Nohr SB, Pedersen KM, Fuglsang E. Iodine nutrition in breast-fed infants is impaired by maternal smoking. Journal of Clinical Endocrinology & Metabolism. 2004; 89: 181-7.

50. Rogahn J, Ryan S, Wells J, Fraser B, Squire C, Wild N, Hughes A, Amegavie L. Randomised trial of iodine intake and thyroid status in preterm infants. Archives of Disease in Childhood Fetal & Neonatal Edition. 2000; 83: F86-90.

51. Matsumura LK, Born D, Kunii IS, Franco DB, Maciel RM. Outcome of thyroid function in newborns from mothers treated with amiodarone. Thyroid. 1992; 2: 279-81.

52. Gandy J, Wonko N, Kantoch MJ. Risks of intravenous amiodarone in neonates. Canadian Journal of Cardiology. 1998; 14: 855-8.

53. Linder N, Davidovitch N, Reichman B, Kuint J, Lubin D, Meyerovitch J, Sela BA, Dolfin Z, Sack J. Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants.[see comment]. Journal of Pediatrics. 1997; 131: 434-9.

54. Yilmaz D, Tezic HT, Zorlu P, Firat S, Bilaloglu E, Kutlu AO. Single dose povidone-iodine on thyroid functions and urinary iodine excretion. Indian J Pediatr. 2003; 70: 675-7.

55. Osborn DA. Thyroid hormones for preventing neurodevelopmental impairment in preterm infants.[update of cochrane database syst rev. 2000;(2):Cd001070; pmid: 10796406]. Cochrane Database of Systematic Reviews. 2001: CD001070.

56. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: A meta-analysis. Ann Intern Med. 2002; 136: 792-801.

57. Zupan J, Garner P, Omari AA. Topical umbilical cord care at birth. Cochrane Database Syst Rev. 2004: CD001057.

58. Mullany LC, Darmstadt GL, Khatry SK, Katz J, LeClerq SC, Shrestha S, Adhikari R, Tielsch JM. Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern nepal: A community-based, cluster-randomised trial. Lancet. 2006; 367: 910-8.

59. Odd DE, Battin MR, Kuschel CA. Variation in identifying neonatal percutaneous central venous line position. J Paediatr Child Health. 2004; 40: 540-3.

60. Odd DE, Page B, Battin MR, Harding JE. Does radio-opaque contrast improve radiographic localisation of percutaneous central venous lines? Arch Dis Child Fetal Neonatal Ed. 2004; 89: F41-3.

61. Reece A, Ubhi T, Craig AR, Newell SJ. Positioning long lines: Contrast versus plain radiography. Arch Dis Child Fetal Neonatal Ed. 2001; 84: F129-30.

62. Rooman RP, Du Caju MV, De Beeck LO, Docx M, Van Reempts P, Van Acker KJ. Low thyroxinaemia occurs in the majority of very preterm newborns.[see comment]. European Journal of Pediatrics. 1996; 155: 211-5.

63. Frank JE, Faix JE, Hermos RJ, Mullaney DM, Rojan DA, Mitchell ML, Klein RZ. Thyroid function in very low birth weight infants: Effects on neonatal hypothyroidism screening. Journal of Pediatrics. 1996; 128: 548-54.

64. Van Wassenaer AG, Kok JH, Briet JM, van Baar AL, de Vijlder JJ. Thyroid function in preterm newborns; is t4 treatment required in infants < 27 weeks' gestational age? Experimental & Clinical Endocrinology & Diabetes. 1997; 105 Suppl 4: 12-8.

65. Ballabio M, Nicolini U, Jowett T, Ruiz de Elvira MC, Ekins RP, Rodeck CH. Maturation of thyroid

function in normal human foetuses. Clinical Endocrinology. 1989; 31: 565-71.

66. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus.[see comment]. New England Journal of Medicine. 1991; 324: 532-6.

67. Radunovic N, Dumez Y, Nastic D, Mandelbrot L, Dommergues M. Thyroid function in fetus and mother during the second half of normal pregnancy. Biology of the Neonate. 1991; 59: 139-48.

68. Reuss ML, Leviton A, Paneth N, Susser M. Thyroxine values from newborn screening of 919 infants born before 29 weeks' gestation. American Journal of Public Health. 1997; 87: 1693-7.

69. Williams FL, Mires GJ, Barnett C, Ogston SA, van Toor H, Visser TJ, Hume R, Scottish Preterm Thyroid G. Transient hypothyroxinemia in preterm infants: The role of cord sera thyroid hormone levels adjusted for prenatal and intrapartum factors. Journal of Clinical Endocrinology & Metabolism. 2005; 90: 4599-606.

70. Franklin RC, Purdie GL, O'Grady CM. Neonatal thyroid function: Prematurity, prenatal steroids, and respiratory distress syndrome. Archives of Disease in Childhood. 1986; 61: 589-92.

71. Reuss ML, Paneth N, Lorenz JM, Susser M. Correlates of low thyroxine values at newborn screening among infants born before 32 weeks gestation. Early Human Development. 1997; 47: 223-33.

72. Rooman RP, Du Caju MV, De Beeck LO, Docx M, Van Reempts P, Van Acker KJ. Low thyroxinaemia occurs in the majority of very preterm newborns. Eur J Pediatr. 1996; 155: 211-5.

73. Paul DA, Leef KH, Stefano JL, Bartoshesky L. Low serum thyroxine on initial newborn screening is associated with intraventricular hemorrhage and death in very low birth weight infants.[see comment]. Pediatrics. 1998; 101: 903-7.

74. Filippi L, Cecchi A, Tronchin M, Dani C, Pezzati M, Seminara S, Gasperini S, Zammarchi E, Rubaltelli FF. Dopamine infusion and hypothyroxinaemia in very low birth weight preterm infants. European Journal of Pediatrics. 2004; 163: 7-13.

75. Belet N, Imdat H, Yanik F, Kucukoduk S. Thyroid function tests in preterm infants born to preeclamptic mothers with placental insufficiency. Journal of Pediatric Endocrinology. 2003; 16: 1131-5.

76. Uhrmann S, Marks KH, Maisels MJ, Kulin HE, Kaplan M, Utiger R. Frequency of transient hypothyroxinaemia in low birthweight infants. Potential pitfall for neonatal screening programmes. Archives of Disease in Childhood. 1981; 56: 214-7.

77. Tahirovic HF. Transient hypothyroxinemia in neonates with birth asphyxia delivered by emergency cesarean section. Journal of Pediatric Endocrinology. 1994; 7: 39-41.

78. Williams FL, Ogston SA, van Toor H, Visser TJ, Hume R. Serum thyroid hormones in preterm infants: Associations with postnatal illnesses and drug usage. Journal of Clinical Endocrinology & Metabolism. 2005; 90: 5954-63.

79. Paul DA, Leef KH, Stefano JL, Bartoshesky L. Thyroid function in very-low-birth-weight infants with intraventricular hemorrhage. Clinical Pediatrics. 2000; 39: 651-6.

80. Hsu CH, Chang JH, Lee YJ, Hung HY, Kao HA, Huang FY. Thyroid function in the sick very low-birth-weight infants.[see comment]. Acta Paediatrica Taiwanica. 1999; 40: 237-42.

81. van Wassenaer AG, Kok JH, de Vijlder JJ, Briet JM, Smit BJ, Tamminga P, van Baar A, Dekker FW, Vulsma T. Effects of thyroxine supplementation on neurologic development in infants born at less than 30 weeks' gestation. New England Journal of Medicine. 1997; 336: 21-6.

82. Brown RS, Bellisario RL, Botero D, Fournier L, Abrams CA, Cowger ML, David R, Fort P, Richman RA. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. Journal of Clinical Endocrinology & Metabolism. 1996; 81: 1147-51.

83. Ogilvy-Stuart AL. Neonatal thyroid disorders.[see comment]. Archives of Disease in Childhood Fetal & Neonatal Edition. 2002; 87: F165-71.

84. Bagis T, Gokcel A, Saygili ES. Autoimmune thyroid disease in pregnancy and the postpartum period: Relationship to spontaneous abortion. Thyroid. 2001; 11: 1049-53.

85. Pekonen F, Lamberg BA, Ikonen E. Thyrotoxicosis and pregnancy. An analysis of 43 pregnancies in 42 thyrotoxic mothers. Annales Chirurgiae et Gynaecologiae. 1978; 67: 1-7.

86. Kriplani A, Buckshee K, Bhargava VL, Takkar D, Ammini AC. Maternal and perinatal outcome in thyrotoxicosis complicating pregnancy. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 1994; 54: 159-63.

87. Zakarija M, McKenzie JM, Hoffman WH. Prediction and therapy of intrauterine and late-onset neonatal hyperthyroidism. Journal of Clinical Endocrinology & Metabolism. 1986; 62: 368-71.

88. Serup J, Petersen S. Hyperthyroidism during pregnancy treated with propylthiouracil. The significance of maternal and foetal parameters. Acta Obstetricia et Gynecologica Scandinavica. 1977; 56: 463-6.

89. Thomas R, Reid RL. Thyroid disease and reproductive dysfunction: A review. Obstetrics & Gynecology. 1987; 70: 789-98.

90. Mitsuda N, Tamaki H, Amino N, Hosono T, Miyai K, Tanizawa O. Risk factors for developmental disorders in infants born to women with graves disease. Obstetrics & Gynecology. 1992; 80: 359-64.

91. Lightner ES, Allen HD, Loughlin G. Neonatal hyperthyroidism and heart failure. A differential approach. American Journal of Diseases of Children. 1977; 131: 68-70.

92. Schonwetter BS, Libber SM, Jones MD, Jr., Park KJ, Plotnick LP. Hypertension in neonatal hyperthyroidism. Am J Dis Child. 1983; 137: 954-5.

93. Oden J, Cheifetz IM. Neonatal thyrotoxicosis and persistent pulmonary hypertension necessitating extracorporeal life support. Pediatrics. 2005; 115: e105-8.

94. O'Donovan D, McMahon C, Costigan C, Oslizlok P, Duff D. Reversible pulmonary hypertension in neonatal graves disease. Ir Med J. 1997; 90: 147-8.

95. Mestman JH. Hyperthyroidism in pregnancy. Endocrinology & Metabolism Clinics of North America. 1998; 27: 127-49.

96. Messer PM, Hauffa BP, Olbricht T, Benker G, Kotulla P, Reinwein D. Antithyroid drug treatment of graves' disease in pregnancy: Long-term effects on somatic growth, intellectual development and thyroid function of the offspring. Acta Endocrinologica. 1990; 123: 311-6.

97. Polak M, Le Gac I, Vuillard E, Guibourdenche J, Leger J, Toubert ME, Madec AM, Oury JF, Czernichow P, Luton D. Fetal and neonatal thyroid function in relation to maternal graves' disease. Best Pract Res Clin Endocrinol Metab. 2004; 18: 289-302.

98. Rink T, Wieg C, Schroth HJ, Helisch A, Bertram U. [hyperthyroidism in a premature infant due to transplacental passage of maternal thyrotropin receptor antibodies]. Nuklearmedizin. 1999; 38: 156-9.

99. Low LC, Lang J, Alexander WD. Excretion of carbimazole and propylthiouracil in breast milk. Lancet. 1979; 2: 1011.

100. Momotani N, Yamashita R, Makino F, Noh JY, Ishikawa N, Ito K. Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. Clinical Endocrinology. 2000; 53: 177-81.

101. Azizi F. Effect of methimazole treatment of maternal thyrotoxicosis on thyroid function in breast-feeding infants. Journal of Pediatrics. 1996; 128: 855-8.

102. Azizi F. Thyroid function in breast-fed infants is not affected by methimazole-induced maternal hypothyroidism: Results of a retrospective study. Journal of Endocrinological Investigation. 2003; 26: 301-4.

103. Azizi F, Hedayati M. Thyroid function in breast-fed infants whose mothers take high doses of methimazole. Journal of Endocrinological Investigation. 2002; 25: 493-6.

104. Azizi F, Khoshniat M, Bahrainian M, Hedayati M. Thyroid function and intellectual development of infants nursed by mothers taking methimazole. Journal of Clinical Endocrinology & Metabolism. 2000; 85: 3233-8.

105. Azizi F, Bahrainian M, Khamseh ME, Khoshniat M. Intellectual development and thyroid function in children who were breast-fed by thyrotoxic mothers taking methimazole. Journal of Pediatric Endocrinology. 2003; 16: 1239-43.

Created: August 2007 A/Prof David Osborn