CONSENSUS GUIDELINES ON 
SCREENING, DIAGNOSIS AND 
MANAGEMENT OF CONGENITAL HYPOTHYROIDISM IN MALAYSIA
**GUIDELINE OBJECTIVES**

The objective is to provide a simplified, practical step-by-step guideline for all health care personnel caring for newborn babies in Malaysia, to ensure

- all newborn babies are screened for congenital hypothyroidism using cord blood at birth or venous blood if cord blood was not available.
- correct interpretation of newborn congenital hypothyroid screening results, appropriate follow-up actions, early diagnosis and treatment of congenital hypothyroidism.
- all healthcare personnel understand the importance and urgency of treatment of congenital hypothyroidism as this is the leading cause of preventable mental retardation in children.

**TARGET POPULATION**

- All newborn babies in Malaysia

**TARGET GROUP**

- Neonatologists
- Obstetricians
- Medical officers
- Paediatricians
- General physicians
- Endocrinologists
- General practitioners
- Family medicine specialists
- Nurses
- All health care workers involved in caring for newborns and infants
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SUMMARY OF RECOMMENDATIONS
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LIST OF ABBREVIATIONS
Thyroid hormone plays a critical role in neurogenesis, myelination and dendrite proliferation of the nervous system in the foetus and newborn. Deficiency of thyroid hormone in congenital hypothyroidism impairs this process resulting in irreversible neurological damage. Early diagnosis via newborn biochemical screening allows the clinician to detect early and initiate thyroxin replacement therapy to prevent neurological damage and mental retardation as well as restore neurocognitive function.

In Malaysia, congenital hypothyroidism affects approximately 1 in 3,000 live births and it is estimated at least 180 babies are born with congenital hypothyroidism each year. Untreated, this can lead to considerable IQ loss in these future adults, and subsequentially cause a reduction of manpower, productivity, and increased burden to the family, society and nation.

Newborn screening for congenital hypothyroidism has been implemented for decades in many countries worldwide. In Malaysia, it has been included in neonatal screening together with G6PD deficiency screening since 2003. Despite the implementation, post-screening management varies between institutions and healthcare facilities. Hence, the standard of care can be erratic due to the complexity of clinical presentations.

The arrival of this document will standardise the quality of care across all healthcare facilities and allow further quality improvement initiatives such as data collection for research and auditing to attune our management strategies and eliminate mental retardation due to congenital hypothyroidism. This document considers the uniqueness of its people and culture, the variable socioeconomic status, the accessibility of medical facilities, the limitation of technology and the paucity of local data. The clinical data gathered will be beneficial to develop treatment, follow-up guidelines, and management strategies that are unique to our local population.

I would like to take this opportunity to extend my congratulations to Dr Wu Loo Ling and her committee of experts, who have taken up this challenge and developed a comprehensive, step-by-step guideline for screening, diagnosis
and management of congenital hypothyroidism in Malaysia. The Ministry of Health is proud to present the first national guideline on congenital hypothyroidism for all healthcare providers hence a testament to the Ministry of Health’s continuous commitment to improving the quality of healthcare for all Malaysian children.

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Cord blood TSH

<20 mIU/L (Normal)
- No further action

20-60 mIU/L (Borderline)
- Cord FT4 >15 pmol/L
- Recall for clinical evaluation and venous TFT
- Cord FT4 ≤15 pmol/L
- Treatment may be considered after collection of venous TFT*

>60 mIU/L (High)
- Recall for clinical evaluation and venous TFT

*In special circumstances such as in disadvantaged families, logistic problems.
TREATMENT ALGORITHM 2

At Recall (Day 4-6)

Check venous TSH and FT4

- TSH <6 mIU/L
  - No further action

- TSH 6-20 mIU/L
  - FT4 >12 pmol/L
  - Repeat TSH, FT4 at Day 8-14

- TSH 20-40 mIU/L
  - FT4 <12 pmol/L
  - Treat
  - Repeat TSH, FT4 at Day 8-14

- TSH >40 mIU/L
  - Treat

Re-check venous TSH, FT4 after 1-2 weeks

- If FT4 low → Treat
- If TSH static beyond 3 weeks and FT4 normal → discuss with parents – start treatment or re-test

- If TSH persistently >20 → Treat
  May consider withhold treatment and re-test if TSH downward trend after discussion with parents and consultation with paediatric endocrinologist.
Congenital hypothyroidism (CH) is the deficiency of thyroid hormone present at birth. It is the most common congenital endocrine disorder and is also the most common preventable cause of mental retardation in children. In the majority of cases, the disorder is permanent and results from either an abnormality in thyroid gland development (dysgenesis, agenesis or ectopia) or a defect in thyroid hormonogenesis. Less commonly, CH is transient and caused by transplacental passage of maternal anti-thyroid drugs, maternal thyrotropin receptor blocking antibodies, maternal or neonatal excessive iodine exposure, low birth weight (LBW), and prematurity. Transient CH usually resolves in the early months of infancy. Very rarely, CH results from a pituitary or hypothalamic abnormality (central or secondary/tertiary hypothyroidism).

Thyroid hormones (TH) play a critical role in the development of multiple organ-systems especially the brain where TH regulates neurogenesis, myelination, dendrite proliferation and synapse formation during foetal and post-natal period. The foetal thyroid develops independently of maternal thyroid status. By 16–20 weeks of gestation, the foetal hypothalamus-pituitary-thyroid axis starts to function and is mature by term. Prior to 16 weeks of gestation, the foetus relies entirely on transplacental delivery of maternal TH. Its supply is controlled by the placenta and maternal TH. After this period, maternal TH continues to buffer foetal thyroid hormones concentration until delivery.

Despite the critical role of TH on foetal brain and multiorgan development, most infants with CH appear normal at birth with no specific signs and symptoms. They are probably protected partly by maternal TH. It had been demonstrated that cord blood free thyroxine (FT4) concentration at birth in CH babies who were unable to synthesize T4 was one third to one half that of normal infants. In addition, there is upregulation of intracerebral type 2 deiodinase activity which converts T4 to T3, leading to an enhanced local supply of active T3 protecting the foetal brain from neurological damage. Hence, normal or near-normal cognitive outcome is possible even in the severely affected infants with CH, provided postnatal replacement therapy is early and adequate. However, when both maternal and foetal hypothyroidism are present, there is significant impairment in neurointellectual development even with adequate replacement therapy soon after birth.
As overt clinical signs and symptoms of CH may only become evident later in infancy accompanied by irreversible neurological damage\(^2\), it is imperative to recognise the diagnosis at birth, so to institute treatment as soon as possible to prevent neurological damage. In this regard, newborn screening programmes had been established in many developed countries in the 1970’s. Many studies had reported success in normalizing cognitive outcomes in children with severe primary CH. In addition, lifetime costs of care for intellectually disabled children are avoided. The estimated cost of neonatal screening is by far less than the cost of diagnosing and treating CH at an older age\(^9\).

Malaysia has an estimated population of 32.6 million and a birth rate of 16.643 per 1,000 population\(^10\). Assuming the incidence of CH to be 1 in 3,000 births, there would have been at least 180 babies born with CH each year in Malaysia. Untreated CH poses a burden to the affected child, family and the nation at large. This is unacceptable as mental abnormality due to CH can be prevented.

In 1998, the Ministry of Health Malaysia launched a pilot project of CH screening based on cord blood thyroid stimulating hormone (TSH) in a few state hospitals in the country. The programme was extended to more hospitals the following year, and in 2003, a nation-wide CH screening programme was implemented in all hospitals. The key performance indices of the programme were to ensure all newborns were screened for CH and treatment instituted promptly.

To date, available local hospital-based studies have reported variable incidences of CH ranging from 1 in 1170 to 3666 live births\(^11,12\). Are we over or under-diagnosing CH? We recognise the challenges faced in Malaysia where resources are limited, and technologies for TH measurements in different laboratories may not be comparable. There are also various logistic or cultural issues resulting in a delay in diagnosis. Some babies miss the initial screening such as babies born before arrival (BBA) to the hospital, lysed or insufficient cord blood. Timing of venous sampling to confirm the thyroid status had been inconsistent. The cut-off values of TSH and free T4 (FT4) were empirical as age-specific reference ranges for the local population are lacking. The management approach to special categories of babies including ill babies in neonatal ICU, premature babies, low birth weight (LBW), multiple births and Down syndrome had not been standardised. The interpretation of neonatal thyroid function is challenging in the light of physiological postnatal surge of TSH, TH and their subsequent rapid decline. It is prudent to understand these changes, the use of appropriate age-specific reference ranges and cut-off values instead of using one range that fits all.
These consensus guidelines aim to ensure coverage of possibly all deliveries, addressing pertinent issues to simplify and standardise screening, diagnosis and treatment of CH in our country. It will take into account available resources in our local setting and provide a step-by-step guidance from screening through to diagnosis, treatment and follow-up of CH in all categories of babies. By standardising practices, we hope to achieve sufficient data to develop our local reference ranges and for future research.
The CH newborn screening programme aims to detect all infants with CH as early as possible with an acceptable cost-benefit ratio, a low false positivity and false negativity. Appropriate management should then be instituted to prevent mental disability.

2.1 Site and timing of sample collection

Recommendations

- Congenital hypothyroid screening using cord blood has been the practice in Malaysia since its implementation on a nation-wide scale in 2003. We would recommend continuation of the same practice, as this is probably the best way to ensure that all newborn babies are screened.

Explanation

Cord blood has been routinely used for the screening of G6PD deficiency in Malaysia. In 1997, congenital hypothyroid screening was added to the existing G6PD programme using the same cord blood sample. This additional screening has been carried out with much success as it has not imposed extra work, time and burden to the busy medical team. Statistics in 2018 had shown that in Malaysia, 99.6% of all deliveries were conducted in hospitals. Hence, screening using cord blood would probably be the most effective way to achieve a near-complete coverage of all deliveries in the country.

However, cord blood sampling may not be viable in some babies e.g. home delivery, BBA, rejected blood due to lysis or insufficient blood sample. For these cases, venous thyroid function test (TFT) should be taken from the baby as soon as possible after the third day of life. This is to avoid the TSH surge that occurs from 1/2 hour after birth to about 72 hours of age, and to ensure early treatment before 2 weeks of life for better prognosis.

2.2 Test strategy

Recommendations

- Primary TSH measurement supplemented by FT4 is the preferred strategy for newborn hypothyroid screening in Malaysia.
• All cord blood will be assayed for TSH level. In babies with borderline high TSH, FT4 would be assayed from the same blood sample.

**Explanation**

Three major strategies for newborn screening are in practice worldwide namely, primary T4 with supplementary TSH, primary TSH with supplementary T4 and combined T4 + TSH. 16

Primary hypothyroidism is by far the commonest cause of CH where TSH is typically high and FT4 low or normal. Hence, TSH screening would be the most sensitive test for early detection and should be the single most important test in any screening programme. 17,18 Delayed diagnosis and treatment of CH results in irreversible brain damage. Disability is greatest in patients who were not treated in the first 3 months of age. 19

Unfortunately, by using TSH as a primary screening tool, there is a likelihood of missing secondary and tertiary hypothyroidism where TSH is low. Nonetheless, CH due to hypothalamic-pituitary deficiency is rare (1 in 50,000-100,000 livebirths). Primary TSH screening approach will also miss thyroxin-binding globulin (TBG) deficiency and more importantly primary hypothyroidism with delayed TSH rise (1 in 100,000 livebirths) due to immaturity of the hypothalamus-pituitary-thyroid axis as in preterm and very low birth weight infants. 20

### 2.3 Interpretation of cord blood TSH and recall of patients

**Recommendations**

- Interpretation of cord blood TSH is as follows:
  - Normal : <20 mIU/L
  - Borderline : 20-60 mIU/L
  - High : >60 mIU/L

- Cord blood TSH >60 mIU/L: Patient should be recalled for clinical evaluation and venous TFT to confirm their thyroid status. In patients whose families are disadvantaged or having logistic issues, consideration may be given to start treatment after venous TFT has been taken.

- Cord blood TSH 20-60 mIU/L: Cord blood FT4 should be measured and taken into account for subsequent action.
  - Cord FT4 ≤15 pmol/L: Patient should be recalled for clinical evaluation and venous TFT.
  - Cord FT4 >15 pmol/L: No further actions are required

- Cord blood TSH <20 mIU/L: No further actions are required
An abnormal screening result should be followed by recall of patient for clinical evaluation and venous blood sampling for re-testing of FT4 and TSH, to confirm the thyroid status\textsuperscript{21}.

Recall of patients for clinical evaluation and venous blood sampling should be done after 72 hours of life, at day 4-6.

In patients where cord blood TSH is not available e.g. home delivery, BBA, rejected blood due to lysis or insufficient blood sample, venous blood should be taken on day 4-6.

Explanation
Stimulation of pituitary TSH and in turn TH secretion is a normal physiologic adaptation to the stress of delivery and extrauterine life. Post-natal surge in TSH occurs within 30 minutes of life followed by FT4, peaking at 24-36 hours of life followed by a rapid decline to reach a steady state by 72 hours\textsuperscript{17,21}. Hence cord blood TSH and TH levels in the newborn must be interpreted in the light of these physiologic changes.

The criteria for interpretation of cord blood TSH results should depend on the frequency distribution of cord blood TSH from the local population. The affected hypothyroid babies usually have TSH values >97.5\textsuperscript{th} percentile of a normal TSH distribution\textsuperscript{22}. Pilot studies in Malaysia have reported cord blood TSH >60 mIU/L in confirmed cases of congenital hypothyroidism\textsuperscript{11,23}. Hence, cord blood TSH >60 mIU/L is considered high and these babies must all be recalled for evaluation to exclude congenital hypothyroidism.

The decision for recall when the cord TSH is borderline (20 to 60 mIU/L) is less clear. Various cut-offs have been used in different studies across the world. The Indian and Sri Lankan guidelines recommend a recall at cord TSH of >20mIU/L for a confirmatory venous thyroid sample\textsuperscript{24,25}.

There are not many studies available on the frequency distribution of cord FT4 levels. Of note, a study in Ethiopia among 123 newborns revealed the 2.5\textsuperscript{th} percentile for cord FT4 was 11.45pmol/L\textsuperscript{26} whereas a similar study in Turkey revealed the 2.5\textsuperscript{th} centile and median as 13.77pmol/L and 16.09pmol/L correspondingly\textsuperscript{27}. The Malaysian National Screening Programme for Congenital Hypothyroidism recommends recall if the cord FT4 is less than 15pmol/L based on initial pilot project data\textsuperscript{13,28}. It is likely that as new local data is available, the cut-off points for the cord TSH and cord FT4 will need to be re-evaluated.
2.4 Communication of abnormal neonatal screening results

**Recommendations**

- There must be a designated staff in-charge of the screening programme at the laboratory, clinic, ward and district health clinic levels.

- There should be an experienced staff overall in charge, overseeing the screening programme and communicating with the family the results of screening and confirmatory tests.

- Detection of an abnormal screening result must be promptly informed by the laboratory staff in-charge of the screening programme to the assigned staff in the clinic or ward to recall patient for clinical evaluation and re-testing to confirm the thyroid status.

- If the patient has already been discharged from the hospital, the family should be contacted urgently by phone.

- The help of the public health nurse at the Maternal and Child Health Clinic nearest to the family should be sought if necessary.

- Blood samples for confirmation of thyroid status should be venous samples and should be taken after 72 hours of life.

**Explanation**

A well-organised team with dedicated staff and adherence to organised standard operating procedure (SOP) is the key to a smooth-running, successful screening programme.

2.5 Clinical evaluation and re-testing for confirmation of thyroid status

**Recommendations**

- All newborns with abnormal screening results must be recalled at day 4-6 for a detailed clinical evaluation and re-testing of FT4, TSH for confirmation of thyroid status.

- Clinical evaluation, which include a detailed history and physical examination, should be conducted by a medical officer.
Evaluation should be focused on determining the signs and symptoms, cause and severity of congenital hypothyroidism. Enquiry into risk factors, features of hypothyroidism and associated congenital abnormalities are emphasised.

**History** – include
› features in the clinical checklist*
› risk factors for congenital hypothyroidism (maternal history of thyroid disease; use of anti-thyroid drug; excessive iodine intake e.g. seaweed; maternal iodine deficiency; parental consanguinity; family history of thyroid disease; prematurity; low birth weight infant; use of iodine anti-septic solutions)

**Physical Examination** – include
› growth parameters
› dysmorphic features
› features in the clinical checklist*
› features of pituitary hormones deficiency (central hypothyroidism)
› congenital malformation e.g. facial mid-line defect (cleft lip, cleft palate, nasal encephalocele), cardiac abnormality particularly atrial and ventricular septal defects, urogenital abnormalities.

*Clinical checklist : Features suggesting congenital hypothyroidism*

- Sluggishness
- Constipation
- Hoarseness of voice
- Poor weight gain
- Dry skin
- Prolonged neonatal jaundice
- Macroglossia
- Umbilical hernia
- Cold extremities
- Wide posterior fontanelle (normal 0.5cm x 0.5cm)
- Goitre

Venous blood is sampled on the same day for re-testing of FT4 and TSH to confirm the thyroid status

**Explanation**
The majority of newborns with CH do not manifest clinical features at birth until 3-6 months later. Clinical features, if present, may be subtle and non-specific. Clinical evaluation should focus on signs and symptoms, associated malformations, risk factors and possible aetiology. Consideration for immediate treatment should be given to patients with symptomatic hypothyroidism.
CH can be isolated or syndromic. Therefore, careful clinical examination is necessary to detect dysmorphic features suggestive of a syndrome. Syndromic CH is mostly caused by mutations in genes encoding transcription factors or involved in early thyroid development. Examples of syndromic CH are Alagille syndrome type 1, Williams–Beuren and DiGeorge syndromes with a high prevalence of thyroid hypoplasia (50-70%) and subclinical hypothyroidism (25-30%)\textsuperscript{32,33}. Pendred syndrome due to mutations in the SLC26A4 gene, with or without goitre, should be considered in cases with sensorineural hearing loss. Besides that, congenital anomalies associated with CH should be sought clinically. These include cardiac defects (particularly atrial and ventricular defects) and urogenital tract abnormalities\textsuperscript{34–36}. Macroglossia may be present within the first weeks and the underlying cause of this is not understood. It does not always respond immediately to treatment but resolves as the infant grows. For Down syndrome see section on Special Categories.
All patients with abnormal cord blood TSH would be recalled on Day 4-6 (after 72 hours of life) for clinical evaluation and re-testing of FT4 and TSH for confirmation of thyroid status. This would include patients whose cord blood TSH was not available, as in home deliveries, BBA, rejected blood samples etc. The venous TFT at Day 4-6 is confirmatory in most cases for diagnosis of CH except in the special categories of babies (see section on Special Categories). In some cases where the results are equivocal, a decision to repeat the test and monitor is a reasonable option after discussion with the parents. FT4 and TSH should not be interpreted in isolation of each other. The suggested thresholds of FT4 in the recommendations only serve as a guide as FT4 concentrations vary significantly with age during the neonatal period, gestation, assay methods and population. Hence, an elevated TSH is often the primary determinant in deciding treatment for primary hypothyroidism.

Recommendations

- **Day 4-6 venous TSH >40 mIU/L**
  - Treatment should be started immediately regardless of FT4 concentration.

- **Day 4-6 venous TSH 20-40 mIU/L**
  - Venous FT4 concentration is taken into consideration.
  - FT4 <12 pmo/L (arbitrary level, expert opinion), treatment should be started.
  - FT4 >12 pmol/L, venous FT4, TSH is repeated within the second week of life (Day 8-14) to re-evaluate.
    - If the repeat TSH on Day 8-14 is persistently >20 mIU/L, treatment should be started. However, when taking into account of all the TSH, FT4 levels and TSH is clearly on the downward trend, decision to withhold treatment and re-test may be considered after discussion with the parents and consultation with a paediatric endocrinologist.

- **Day 4-6 venous TSH 6-20 mIU/L**
  - Venous TFT is repeated after 1-2 weeks
  - Treatment is indicated if the repeat venous FT4 falls below age-specific reference range.
If TSH remains static within 6-20 mIU/L after the age of 21 days in a healthy neonate with a normal FT4, options should be discussed with parents whether to start treatment, or to withhold treatment and to re-test 1-2 weeks later to re-evaluate the need for treatment (lack of evidence in favour or against treatment).

- **Day 4-6 venous TSH <6 mIU/L** – Normal thyroid function. No further action is required.

**Explanation**

Postnatal physiological surge of TSH and FT4 declines rapidly in the first 3 days of life, followed by a gradual decline after one month old\(^2\)\(^,\)\(^3\)\(^7\)\(^,\)\(^4\)\(^6\). Hence, confirmatory venous TFT is best taken after 72 hours of life. In Malaysia, this is done on Day 4-6 of life.

The physiological surge and decline in TSH and FT4 in the neonatal period make interpretation of these hormone levels during this period, challenging. In addition, babies with primary CH who are born premature, or with low birthweight, or who are sick in the neonatal period may not be able to generate an adequate TSH response in the first weeks of life (refer to section on Special Categories). Hence, it is prudent to know the gestation and post-natal age of the newborns and use the appropriate age-specific reference ranges in the interpretation of TFT. There are notable differences in reference ranges for TSH and more so for FT4 from different laboratories and various study reports due to differences in population, assay methods and manufacturer instruments\(^3\)\(^8\)\(^-\)\(^4\)\(^9\). In Malaysia, local age-specific reference ranges are lacking, the threshold values recommended in this guideline are based on experience and expert opinion. The trends of TSH and FT4 are important pointers to guide us in our decision to treat or to monitor. However, decision to err towards treatment may be reasonable in cases where there are logistic issues which may hinder early treatment e.g. turnaround time for TFT result is unpredictable or prolonged, or disadvantaged families that do not have easy access to the hospital or clinics.

In the early phase of newborn screening in Japan, initiation of treatment was often delayed until 4–5 weeks of life and patients with CH were found to have a lower IQ in comparison with controls\(^3\)\(^9\)\(^,\)\(^5\)\(^0\). Hence, timing of normalization of TH is critical for brain development in the infant and prompted treatment of CH within the first 2 weeks of life for optimal neurocognitive outcome\(^3\)\(^7\)\(^,\)\(^3\)\(^9\)\(^,\)\(^5\)\(^0\)\(^-\)\(^5\)\(^5\). In the vast majority of early and adequately treated children with CH, neurodevelopmental and school outcomes are normal and intellectual disability virtually disappeared\(^5\)\(^0\)\(^-\)\(^5\)\(^5\). Treatment for CH should be started immediately if venous TSH concentration is >40 mIU/L after 72 hours of life because this value strongly suggests decompensated hypothyroidism, which is generally agreed among international consensus\(^3\)\(^7\). If TSH concentration is
<40 mIU/L with a normal FT4 concentration for age-reference, the clinician may postpone treatment pending the repeat TFT (expert consensus opinion). Treatment is indicated if TSH concentration is persistently >20 mIU/L in the 2nd week of life even if serum FT4 concentration is normal, keeping in view that this is an arbitrary threshold based on expert opinion37.

Whether healthy neonates with mildly elevated TSH concentrations between 6-20 mIU/L beyond 21 days but a normal FT4 concentration benefit from L-thyroxine (LT4) treatment is still unclear with lack of evidence in favour of or against treatment. The European Society for Paediatric Endocrinology consensus guidelines suggests to either start treatment immediately and retest, then stop treatment at a later stage, or to re-test 1-2 weeks to re-evaluate the need for treatment1. Discussion with the family, the trend of the TSH and FT4 concentrations and clinical judgement will be instrumental to decide whether to treat or not. In many cases the TSH will decrease spontaneously into the normal range2,38,40 but, if the FT4 concentration falls below age-specific reference range or TSH remains persistently raised, treatment with LT4 is likely to be required.

In patients with a clear diagnosis of CH based on biochemistry, treatment should not be delayed for imaging. Ultrasound is useful to determine the presence of the thyroid gland and its location and size. This non-invasive imaging, however, is operator dependent. Thyroid scintigraphy is useful to detect a hypofunctioning or an ectopic thyroid gland when it is not visualized on ultrasound37. However, at present, it is not routinely done in our local setting in early infancy due to its limited availability, but considered at re-evaluation at an older age above 3 years old. A knee x-ray may be performed to assess the severity of intrauterine hypothyroidism37,39. A lack of a bilateral or unilateral distal femoral nucleus on the radiograph of a mature infant at ≥38 weeks gestational age indicates a lack of thyroid hormone in the foetal stage39.
Early initiation of thyroid hormone treatment is critical to prevent mental retardation and to restore IQ as well as neurodevelopment. Treatment initiation within 2 weeks of life had shown restoration to near-normal IQ in moderate and severe CH\textsuperscript{56}. Delayed treatment by one week causes a significant reduction in IQ by approximately 10 points\textsuperscript{57}. It is noteworthy that despite early initiation of treatment, a delayed normalization of FT4 could also affect the child’s neurodevelopment adversely\textsuperscript{51}. Two main factors which had been shown to influence cognitive outcome in CH are - 1) age at start of LT4, and 2) the starting dose of LT4\textsuperscript{52}. Therefore, treatment of CH should aim at early treatment and rapid normalization of FT4, followed by appropriate dose adjustment to prevent under or over treatment. Practical measures should be taken to ensure compliance, adequate dosing and absorption of the medication.

4.1 Treatment of congenital hypothyroidism

Recommendations

- Treatment should be started as soon as diagnosis is made.
- LT4 is the treatment of choice for CH.
- An initial dose of LT4 at 10-15 mcg/kg/day (maximum 50 mcg/day) is recommended, the lowest dose for mild disease and higher dose for severe disease.
  - Mild CH (FT4 >10 pmol/L) 10 mcg/kg/day
  - Moderate CH (FT4 5–10 pmol/L) 10 mcg/kg/day
  - Severe CH (FT4 <5 pmol/L) 15 mcg/kg/day
  - Subclinical CH 5-10 mcg/kg/day
- A brand LT4 rather than a generic formulation is recommended especially in the first 3 years of life.
- LT4 should be dispensed in tablet form. LT4 in suspension or syrup form is not recommended. In rare cases where oral administration is not possible, intravenous administration can be considered with IV dose that is no more than 80% the oral dose\textsuperscript{37}.
• LT4 tablets can be crushed, mixed in small amount of water or milk, and served using a spoon. LT4 should not be served in a milk-bottle.

• Timing of LT4 administration should be consistent every day to ensure compliance. We recommend taking the medication in the morning upon awakening for all ages (expert consensus opinion). LT4 can be taken before, with or after food. However, intake of soy, iron or calcium supplementation within an hour of LT4 administration should be avoided.

Explanation
Cerebral and neuronal development in the foetus continues into the postnatal period. T4 plays a key role in this process. During the intrauterine period, the serum T4 of the CH foetus is buffered by maternal T4. After birth, serum T4 drops in the CH newborn. Hence, it is imperative to initiate LT4 treatment as soon as possible in order to rapidly restore serum T4, to shorten the period of hypothyroxinaemia to prevent neurological damage. TSH may take a longer time compared to T4 to normalise.

Severity of CH is defined as mild, moderate and severe according to the pre-treatment serum FT4 levels of >10 pmol/L, 5-10 pmol/L and <5 pmol/L respectively. A higher initial dose of LT4 up to 15 mcg/kg/day is preferred for severe CH while lower dose is recommended for the mild to moderate CH. In infants with pre-treatment FT4 within the age-specific reference range and elevated TSH i.e. subclinical hypothyroidism, an even lower initial LT4 dose of 5-10 mcg/kg/day may be considered. Higher initial dose of LT4 leads to more rapid normalization of thyroid hormones and possibly improved intellectual benefits. However, some studies disagree with higher doses which result in significantly higher overtreatment rates, and hence suggest narrower dosage range between 7-10 mcg/kg/day at initial diagnosis. It is important to re-evaluate FT4 and TSH 1-2 weeks after initiation of treatment to fine-tune the LT4 dosage to prevent over-treatment. In any case if intravenous treatment is required, the starting dose should be no more than 80% of the oral dose.

It has been reported that brand and generic LT4 were not bioequivalent in patients with severe hypothyroidism. Hence, to ensure adequate and optimal replacement, the use of brand LT4 is recommended especially in the severe cases of CH and those younger than 3 years of age, which is the window-period of critical brain development. However, another study which was retrospective noted no difference between brand and generic formulations.

Syrup or suspension forms of LT4 should not be used for the treatment of CH due to uncertainty of the stability of the formulations and unreliability in measurement of correct dose each day. However, studies have shown conflicting results comparing tablets and liquid formulations with regards to efficacy. In most countries, only the tablet form of LT4 is recommended.
and it is the most widely available form in our country. Ideally, the medication should be served using a spoon rather than in the milk bottle. This is to ensure that the infant consumes the full dose of the medication.

LT4 is administered orally in a single daily dose. The European Society for Paediatric Endocrinology and the Japanese Society for Paediatric Endocrinology proposed that LT4 should be administered at the same time everyday either in the morning or evening, irrespective of fasting state\textsuperscript{37,59}. However, an adult study reported that administration of LT4 at bedtime is more effective in terms of thyroid hormone levels than in the morning\textsuperscript{69}. No paediatric study is available to date. The Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society recommends that although the absorption of LT4 may be better on empty stomach than with or after meals, consistent timing of medication and regular re-evaluation of thyroid function with appropriate dose adjustment are more important in the treatment of hypothyroidism\textsuperscript{70}.

Substances like soy protein, iron and calcium may interfere with LT4 absorption\textsuperscript{1,58,71}. Hence, these substances should be consumed at different times from the LT4 to ensure optimal absorption and treatment outcome. On the other hand, hypersensitivity to vitamin D with hypercalcaemia has also been reported in infants with CH treated with LT4\textsuperscript{72}.

### 4.2 Monitoring treatment of congenital hypothyroidism

**Recommendations**

- Serum FT4 and TSH should be measured before, and at least 4 hours after the last LT4 administration. If timing of blood taking and LT4 administration clashes, LT4 should be delayed until blood has been taken for TFT.

- After initiation of LT4, the first clinical and biochemical follow-up evaluation should be 1-2 weeks later. If the initial dose of LT4 is close to 15 mcg/kg/day or 50 mcg/day, follow-up evaluation should be earlier, within 1 week of treatment initiation.

- Subsequent clinical and biochemical evaluation should be every 2 weeks until TSH normalises.

- Thereafter, the evaluation can be reduced to every 1 to 3 months until the age of 12 months.

- Between the ages of 1 and 3 years, the frequency of evaluations can be lowered to every 2 to 4 months; thereafter, every 3 to 6 months until growth is completed.
• Serum concentration of TSH should be kept within the age-specific reference range and FT4 or total thyroxine (TT4) in the upper half of the age-specific reference range. Over-suppression of TSH to <0.5 mIU/L should be avoided.

• Adjustment of LT4 dose should not be based on a single reading of FT4 (or TT4) or TSH. FT4 and TSH should be interpreted together and not in isolation. If FT4 is slightly above the upper limit of normal range with normal TSH, it is safe to continue the same dose of LT4 unless patient manifests symptoms of hyperthyroxinaemia.

• Evaluations should be performed at more frequent intervals if abnormal FT4 or TSH are found or if compliance is questioned.

• After any change in LT4 dose or LT4 formulation (e.g. switching from brand to generic LT4), extra follow-up evaluations should be done 4 to 6 weeks later until FT4 and TSH are normalised.

• Adequate TH replacement throughout childhood is important. Over-treatment or under-treatment when TSH is out of reference range should be avoided.

• The incidence of adverse events during LT4 treatment is very low. However, careful monitoring is recommended to minimise risk.

**Explanation**

Once started with LT4 replacement, neonates should have their thyroid function repeated in 1-2 weeks until TSH levels are normalised (1 week at the latest in case of starting with higher dose). This is to ensure rapid normalisation of thyroid levels especially in neonates with severe cases of CH and high doses of thyroxine was used, and to avoid overtreatment. Rapid normalisation of thyroid hormone and maintenance of relatively higher FT4 concentrations during the first year of life leads to a better intellectual outcome. TSH normalises slower compared to FT4. Hence, the first goal is to rapidly achieve normalisation of FT4 (within 2 weeks of treatment). The second treatment goal is the normalisation of TSH within 4 weeks of treatment.

Frequent monitoring of TSH and FT4 is required in neonates and young infants who are on LT4 treatment. Depending on the lab assays and sensitivities, the TSH levels should be kept between 0.5-5.0 mIU/L. TSH and FT4 level may vary from one assay to another and appears to have lack of standardisation.
FT4 or TT4 should be analysed and interpreted together with TSH. Adjustment of LT4 doses should not be based on serum T4 alone, to prevent the occurrence of prolonged periods of supraphysiological TH\textsuperscript{60,77,78}.

Adequate treatment of CH minimises the risk of treatment-related adverse effects\textsuperscript{79-81}. Close monitoring with biochemical parameters is aimed to avoid over- or under-treatment. Adverse effects of long-term LT4 treatment are therefore rare or even absent if the treatment has been adequately prescribed\textsuperscript{62}. Reports on pseudotumour cerebri or craniosynostosis have been previously described\textsuperscript{79,82}. One study reported a cohort of CH patients with period of overtreatment between 6 to 9 months of life, who showed relative macrocrania but without craniosynostosis at the age of 18 months\textsuperscript{83}. On the other hand, another cohort of young adults with CH was reported to have cardiovascular abnormalities i.e. impaired diastolic function, exercise capacity and increased intima media thickness. However, the clinical relevance of these findings are not known to date\textsuperscript{84}. Interestingly, a cohort study of 61 patients showed that overtreatment during the first two years leads to lowered cognitive outcomes at 11 years, while undertreatment resulted in a normal cognitive development\textsuperscript{85}. 
In Malaysia, practically all cases of CH are started on thyroxine replacement after biochemical confirmation of hypothyroidism, without prior imaging studies of thyroid scintigraphy or thyroid ultrasonography. Treatment is initiated based on functional status of the thyroid gland; the aetiology and permanence of the CH are often not established at diagnosis.

Imaging studies are useful tools to determine aetiology, function and permanence of CH. An abnormal thyroid gland detected on imaging study e.g. abnormal location of the gland (lingual thyroid, ectopic thyroid) or abnormal structure (athyreosis, hypoplasia, dysplasia, anatomical defect) are indicators of permanent form of CH and treatment will be life-long. On the contrary, a normally located thyroid gland i.e. gland-in-situ (GIS), with normal structure is often associated with a transient form of CH whereby the thyroid function recovers spontaneously and treatment may be discontinued.

Without imaging studies at diagnosis, all babies treated for CH will need to be re-evaluated. The aim of re-evaluation is to determine if the CH is permanent or transient and to establish the aetiology. Thyroxine treatment would then be discontinued in those with transient CH but continued in those with permanent CH. Hence the essential steps at re-evaluation would be to stop the thyroxine treatment, followed by re-testing of thyroid function. In those who have persistent hypothyroidism at re-evaluation, imaging studies may be considered to define the aetiology.

5.1 Re-evaluation of thyroid function

Recommendations

- Re-evaluation of thyroid function is performed on all CH in whom the aetiology and permanence of CH has not been established before initiation of thyroxine replacement i.e thyroid scintigraphy has not been done.

- Re-evaluation is done at or after 3 years of age when myelination in the central nervous system is complete.

- At re-evaluation, thyroxin is stopped for 4 weeks or phased out over 4-6 weeks duration. At the end of this period, venous FT4 and TSH are measured (see section 5.2 for interpretation of results)
• Re-evaluation is particularly important in CH where previous ultrasonography (if done) had demonstrated a GIS or eutopic thyroid gland, as well as in babies with risks of transient CH and babies with presumed isolated central CH.

• Early re-evaluation may be considered in a CH child who has a GIS and requires a low thyroxine dose of less than 3 mcg/kg/day at the age of 6 months, as they are likely to have a transient form of CH. Re-evaluation can be done at or after the age of 6 months.

• Re-evaluation for the need of long term thyroxine therapy may not be required if venous TSH has been persistently >10 mIU/L after 1 year of age despite thyroxine replacement, as this most likely indicates a permanent form of CH.

• In patient confirmed to have permanent form of CH at re-evaluation, thyroid ultrasonography should be considered to determine the aetiology of CH if this has not been done previously. Thyroid scintigraphy may also be considered if necessary for definitive aetiological diagnosis.

Explanation
In Malaysia, thyroid scintigraphy is not routinely done prior to initiation of thyroxine replacement therapy, due to limited resources and lack of expertise in this imaging modality on newborn babies. Almost all CH babies in Malaysia are treated with thyroxine at diagnosis without prior imaging studies.

Re-evaluation of the thyroid axis is therefore important, as about 30-40% of CH cases are transient. Transient CH may be due to maternal hypothyroidism, maternal antithyroid drug use and/or thyroid autoantibodies, maternal iodine deficiency, prematurity, low birth weight or critically ill babies. Transient hypothyroxinaemia in prematurity is caused by immaturity of the hypothalamus-pituitary-thyroid axis and this is further aggravated in a sick premature infant resulting in low production of TH. Maternal iodine deficiency also causes transient CH due to poor foetal and neonatal iodine stores. In maternal thyroid disease, the use of antithyroid drugs on the mother causes transient neonatal hypothyroidism up to 2 weeks from birth. Thyroid blocking antibodies from the mother can last up to 3 to 6 months in the infant, resulting in transient hypothyroidism. In these babies, their thyroid functions normalise after approximately 6 months of age.

The ideal timing of thyroid re-evaluation is at or after 3 years of age as the myelination in the central nervous system completes by 36 to 40 months. However, recent studies have shown that thyroid re-evaluation for the need of thyroxine therapy can be considered as early as 6 months of age onwards in patients with a GIS or eutopic thyroid gland and who are on low doses of...
thyroxine therapy. In a study by Saba et al,\textsuperscript{90} the thyroxine dose cut off for predicting transient CH was 3.2 mcg/kg/day and 2.5 mcg/kg/day at 6 and 12 months respectively. 54\% of 92 patients with GIS were found to have transient CH. In another study by Oron et al,\textsuperscript{91} 20\% of 84 patients with a GIS had transient CH at a cut off thyroxine dose of 2.2 mcg/kg/day at 6 months of age.

Thyroid ultrasonography is useful to determine the presence, location and anatomy of the thyroid gland. However its accuracy is operator dependent. Thyroid scintigraphy is the more reliable imaging modality to determine the aetiology of CH, especially in cases of thyroid dysgenesis and dyshormonogenesis. The combination of thyroid ultrasonography and scintigraphy provides both anatomical and functional information\textsuperscript{92}. Genetic test can be considered in familial causes of CH but this test is not available routinely in Malaysia.

5.2 Outcome of re-evaluation

Recommendations

- If FT4 & TSH are within the normal reference range without thyroxine replacement for 4 weeks, this likely indicates transient CH. Thyroxine replacement is discontinued and thyroid function monitored for the next 6 months. If thyroid function remains normal after 6 months of follow-up, the patient can be discharged.

- If TSH is >10 mIU/L without thyroxine replacement for 4-6 weeks, this likely indicates permanent CH. Thyroxine replacement is resumed. The patient continues regular follow-up with periodic clinical and biochemical evaluation to ensure FT4 and TSH are within reference range.

- If TSH is <10 mIU/L, but more than upper limit of reference range and FT4 normal, the period without thyroxine replacement is extended for another 3-4 weeks. FT4 & TSH are re-tested at the end of the extended period. Long term thyroxine replacement is indicated if structural abnormality of the thyroid gland is present, or TSH increases to >10 mIU/L, or FT4 falls to below the reference range for age, or there are symptoms and signs of hypothyroidism.

Explanation

In a study by Rabbiosi et al,\textsuperscript{93} the features and outcome of CH patients with a GIS or eutopic thyroid gland, who underwent re-evaluation at the age of 3 years were analysed. 38.1\% of patients had transient hypothyroidism, whereby thyroid function was normal after stopping thyroxine for at least 1 year of follow-up. 34.5\% of cases showed permanent CH whereby TSH increased.
over 10mIU/L while 27.4% of cases showed subclinical hypothyroidism, whereby TSH was 5-10mIU/L during follow up. Thyroid hypoplasia was detected in 13.7% of patients with permanent hypothyroidism and 4.5% of patients with subclinical hypothyroidism, but not in any patient with transient hypothyroidism.

Subclinical hypothyroidism is defined by serum TSH above the upper normal reference range with normal FT4 levels. While there is general agreement to initiate treatment when TSH is >10mIU/L, the decision to start treatment in mild subclinical hypothyroidism where TSH is 4.5-10 mIU/L is still debatable\textsuperscript{94}. Current data shows that patients with mild subclinical hypothyroidism have normal linear growth\textsuperscript{95,96}, bone health\textsuperscript{97} and intellectual outcome\textsuperscript{98}. However, subtle pro-atherogenic abnormalities in lipid profile\textsuperscript{99,100} and mild deficits in specific cognitive domains\textsuperscript{101,102} have been reported in some cases of persistent TSH elevation. Children with mild subclinical hypothyroidism need to be regularly monitored to ensure the early detection of those who may benefit from treatment.
Patients with CH should be monitored for the following outcomes from the time of diagnosis. Adequate thyroxine replacement and strict adherence to treatment is vital to ensure optimal long-term outcome of CH. Regular follow-up is emphasized so that any deviation from normal may be detected early and corrected.

### 6.1 Neurodevelopment

**Recommendations**

- Neurodevelopment (particularly psychomotor and speech development) and school performance should be monitored during follow-up, especially in those with severe CH, delayed treatment and poorly controlled CH particularly during the first year of life and those from economically disadvantaged families.

- For CH with speech delay and problems in learning, attention, memory and behaviour, referral to allied health team (e.g. child psychologist, speech therapist) for further evaluation and therapy should be considered.

- Hearing tests should be performed before school age and repeated if hearing impairment is suspected.

- Adequate treatment throughout childhood is essential and overtreatment should be avoided.

**Explanation**

Thyroid hormone deficiency has adverse effects on foetal and postnatal brain development, causing brain damage\(^{103}\) manifesting as developmental delay and intellectual disability (defined as IQ < 70) in untreated CH\(^{55}\). Universal newborn screening in high-income countries since 1970s with early treatment has eradicated and prevented intellectual disability\(^{55}\). However, despite early adequate treatment of CH, there were reports of subnormal cognitive and motor development during childhood\(^{104}\).
Studies on developmental and cognitive outcomes at different ages from first year till teenage in early treated CH revealed that severe CH patients had lower developmental and IQ scores\textsuperscript{105-111}. This may be due to prenatal brain damage which is not reverted by optimal postnatal treatment\textsuperscript{112}. Children with CH may have brain abnormalities that account for the subtle and specific deficits in memory, language, sensorimotor, and visuospatial function\textsuperscript{113,114}.

The vast majority of early and optimally treated CH patients have normal neurodevelopmental and school outcomes and are well integrated into society\textsuperscript{52,104}. However, inadequate treatment in infancy and childhood related to medication adherence problems can adversely affect cognitive outcome and school performance\textsuperscript{115}. Lower parental socioeconomic status was also associated with poorer neurodevelopment and cognitive outcomes\textsuperscript{108,109}. Other causes of developmental delay and cognitive impairment should be considered in CH patients who are treated early and adequately.

Behavioural problems and attention deficits are reported at school age in CH, particularly in those who were overtreated within the first 6 months of life\textsuperscript{116-118}. Undertreatment in the period 3-6 months postnatal and in patients with severe CH, is associated with autism features at primary school age\textsuperscript{116}. However, a vast majority of the CH patients do not have a diagnosis of attention-deficit hyperactivity syndrome or autism\textsuperscript{116}.

TH plays a role in cochlear development and auditory function. Hearing impairment will adversely affect speech development, school performance, and social interactions. Permanent sensorineural hearing loss has been reported in CH patients who are diagnosed and treated late in infancy before the age of 6 months but outside the neonatal period\textsuperscript{104}.

Hearing problems remain despite newborn screening programs. For CH treated early in the neonatal period, mild sensorineural hearing impairment was still reported in childhood and young adulthood\textsuperscript{119,120}. Those with severe CH are at higher risk of significant hearing impairment\textsuperscript{120}. Hearing impairment observed in early-treated CH may be due to mild progressive hearing loss that is not severe enough for detection during the neonatal period until early childhood\textsuperscript{104}.

In the follow-up, more attention should be given to those with severe CH as they are at higher risk of poorer neurodevelopment and cognitive outcomes, behavioural problems and hearing impairment later in childhood and adulthood. Sustained attention problems related to episodes of overtreatment have been reported\textsuperscript{118,121}. 
6.2 Growth and puberty

**Recommendations**
- Growth and puberty should be monitored.
- Parents and patients should be informed that growth and puberty are normal in adequately treated non-syndromic CH.

**Explanation**
Thyroid hormone is essential for normal skeletal growth and maturation in the postnatal period. Untreated hypothyroidism causes poor linear growth and abnormal puberty (pubertal delay or precocious puberty).

Various studies in different countries have shown that early treated CH have normal growth, puberty and final adult height\(^ {122-124}\). Menarche and menstrual cycles are also normal\(^ {108}\). Final height is not affected by severity and initial treatment of CH, if adequately treated with LT\(4\)\(^ {122,125}\).

6.3 Metabolic, cardiovascular and bone health

**Recommendations**
- Parents and patients should be informed that metabolic, cardiovascular and bone health in CH are normal if treatment is adequate with good adherence.
- Healthy lifestyle with healthy diet and regular exercise should be emphasised to optimise weight and health.
- Body mass index should be monitored to detect overweight & obesity early, so that lifestyle intervention can be instituted and intensified.
- Adherence to thyroxine treatment during adolescence should be emphasized for future cardiovascular health.

**Explanation**
Body mass index (BMI) and body composition are generally normal in children and young adults with adequately treated CH\(^ {51,52}\). However, CH is associated with increased risks of overweight or obesity in childhood and adulthood as adiposity rebound at a younger age is observed in CH\(^ {106,126,127}\). Early adiposity rebound is associated with adult obesity\(^ {126}\). Obesity and its associated complications such as type 2 diabetes mellitus, hypertension, early cardiovascular diseases are increasingly prevalent problems in Malaysia\(^ {128,129}\). Therefore, lifestyle intervention should be encouraged in CH to prevent obesity and metabolic complications.
TH affects cardiovascular function. Young adults with adequately treated CH have normal blood pressure, glucose & lipid profiles and carotid intima-media thickness (a marker of atherosclerosis)\(^80\). However, subclinical cardiovascular changes and dysfunction have been reported in young adults with CH, especially those with uncontrolled hypothyroidism during puberty\(^80,130\). It is unclear if these subtle abnormalities result in an increased risk of cardiovascular disease.

TH affect bone remodelling. Studies in children and young adults with CH have shown normal bone mineral density after prolonged LT4 therapy\(^131,132\).

### 6.4 Health-related quality of life (QOL)

**Recommendations**

- Parents and patients should be informed that patients with CH can expect to lead a normal life in adulthood in terms of physical health, social functioning and mental health if treatment is adequate with good adherence throughout life.

**Explanation**

Abnormal thyroid function can affect mood, emotion, behaviour, neurosensory and cardiovascular functions, and impact long-term health and social functioning\(^104\). There are reports of reduced health-related QOL in CH children & young adults with respect to cognitive and social functioning, emotions, self-esteem and physical health\(^133-135\). In contrast, there are studies showing no difference in health-related QOL scores in young adults adequately treated for CH compared to the healthy population\(^52,136\). The risk of having reduced health related QOL, particularly in mental dimensions appear to be higher with severe CH and presence of inadequacy of long-term treatment\(^104\).

### 6.5 Fertility & future pregnancy outcome

**Recommendations**

- Parents and post-pubertal patients should be informed that fertility is normal in adequately treated CH.

- Parents and post-pubertal patients should be informed that normal thyroid hormone status is vital for optimal pregnancy outcome and foetal neurodevelopment. Adherence to treatment and more intensive monitoring of thyroid status are essential during pregnancy.
**Explanation**

Age at menarche and menstrual cycles are normal in adequately treated CH\(^{104,123}\). Fertility is normal in both men and women with CH, except in women with severe CH\(^{137}\).

TH requirement increases during pregnancy. Maternal hypothyroidism during pregnancy is associated with obstetric problems and adverse neurocognitive outcome in the offspring, especially if it occurs early in pregnancy as the developing foetus relies solely on maternal thyroid hormone in the first trimester for normal neurodevelopment. Women with uncontrolled CH during pregnancy have higher risk of gestational hypertension, emergency caesarean delivery, preterm delivery and foetal macrosomia\(^{138}\).

Children of women with CH have been reported to have lower developmental scores at one year of age compared to the normal population, especially if there was uncontrolled maternal hypothyroidism\(^{139}\).
The following groups of neonates are at high risk for later development of congenital hypothyroidism post-screening. Even though they may have passed their initial screening, they should have their thyroid function test repeated.

- Sick neonates
- Preterm infants/low birth weight
- Down syndrome
- Multiple births
- Infant of mother with autoimmune thyroid disease
- Prolonged neonatal jaundice
- Congenital central hypothyroidism

### 7.1 Sick neonates

Sick neonates include newborns with perinatal asphyxia, sepsis or critically ill requiring respiratory and cardiovascular support, and newborns who have undergone major surgery.

**Recommendations**

- Repeat venous FT4, TSH is recommended about 2 weeks after recovery from illness, irrespective of the initial screening results.
- Treatment of sick neonates with isolated hypo thyroxinaemia with LT4 is not recommended.

**Explanation**

Many sick neonates manifest sick euthyroid syndrome in which the FT4 is slightly low or normal, and TSH is slightly high. Sick euthyroid syndrome occurs in 60.7% of term babies with sepsis, 54.2% and 80.9% in pre-term with early and late sepsis respectively. Prolonged sepsis lasting more than 8 days is associated with both low T3 and T4 in 29.5% of sick term babies. The abnormal thyroid function in sick euthyroid syndrome is an adaptive response to stress-related increase in cytokines and other inflammatory mediators. Drugs such as dopamine, dobutamine, caffeine, morphine and glucocorticoids used in these sick neonates, as well as the excessive use of iodine for multiple aseptic procedures interfere with thyroid hormone production, contributing to hypo thyroxinaemia.
As sick euthyroid syndrome is an adaptive response to reduce tissue metabolism and to preserve energy, treatment with LT4 is currently not recommended and may result with detrimental effects on babies\textsuperscript{143}. Spontaneous normalization of thyroid function is expected after recovery from illness\textsuperscript{2}.

7.2 Preterm infants/low birth weight (LBW)

CH may be missed in preterm (<37 weeks) and LBW (<2.5kg) babies because of delayed and blunted post-natal TSH rise in these babies. The level of initial cord blood TSH in preterm/LBW may not be high enough to be detected by the cut-off level of TSH. Hence post-screening repeat thyroid function tests should be considered.

Recommendations

- In late preterm, 34 to <37 weeks, TFT should be repeated 2 weeks after initial screening. Venous sampling may be done at the Maternal and Child Health Clinic (MCHC) nearest to their homes.

- In preterm <34 weeks who are not admitted or had only a short stay in the hospital, TFT should be repeated 2 weeks after the initial screening.

- In preterm < 34 weeks who has a prolonged stay in the hospital due to prematurity, TFT should be repeated at 2-weekly intervals until discharge and 2 weeks post discharge.

- In LBW <2.5 kg, TFT should be repeated 2 weeks after initial screening. If these babies are admitted to the hospital, TFT should be done at 2-weekly intervals until discharge and 2 weeks post discharge.

- LT4 therapy of isolated hypothyroxinaemia without clear elevation of TSH is not recommended.

Explanation

Post-natal TSH surge in the premature or LBW babies is blunted, predominantly due to immaturity of the hypothalamic-pituitary-thyroid axis\textsuperscript{144}. This in turn leads to hypothyroxinaemia at birth which is common, occurring in approximately 1:300 preterm babies <1500 g at birth\textsuperscript{145}. Preterm babies have lower serum T4 at birth which rise subsequently to match the T4 levels of term babies by 4-8 weeks of post-natal age. 50\% of preterm infants born at <33 weeks of gestation who were diagnosed with congenital hypothyroidism had delayed TSH elevation and would not have been detected on first newborn screen\textsuperscript{145}. Moreover, they have relatively low TSH levels according to corrected gestational age\textsuperscript{147}. Hence screening based on TSH strategy may miss the
diagnosis of congenital hypothyroidism in a large proportion of the preterm and LBW babies. One half of the preterm babies which include LBW (1.5-2.5kg), VLBW (1.0-1.5kg) and ELBW (<1.0 kg), who were later diagnosed to have congenital hypothyroidism were not diagnosed based on initial screening test\textsuperscript{146}. Among VLBW newborns with primary CH, only 3\% would have been treated with LT4 based on their initial thyroid screening at birth\textsuperscript{146}.

Other causes of delayed TSH rise and hypothyroxinaemia of prematurity include non-thyroidal illnesses, use of drugs known to suppress TSH, decreased hepatic production of thyroid-binding globulin, poor iodine store, the loss of transplacental maternal thyroxine and multiple use of topical iodine for aseptic procedures. To date, there is insufficient evidence to determine whether treatment of preterm infants with low TH and normal TSH, results in changes in neonatal morbidity and mortality\textsuperscript{148}.

7.3 **Down syndrome (DS)**

DS has a higher incidence of congenital hypothyroidism than the general population with a reported rate of 1: 50 to 140 DS patients\textsuperscript{149,150}. This hypothyroid state is thought to be due to a developmental defect of the thyroid gland or DS-specific thyroid hypoplasia\textsuperscript{151-153}. Besides this, thyroid function in DS may be further complicated by the co-existence of cardiac and/or gastrointestinal abnormalities leading to a false negative screening result.

**Recommendations**

- TFT should be repeated at 3-4 weeks of life even if the initial screening result is normal.

**Explanation**

A mild hypothyroid state may occur as early as first week of life in DS\textsuperscript{154}. Unfortunately, mildly elevated TSH may not be detected by the routine cut-off value used in screening for CH. Therefore, we advocate to repeat TFT before the end of the neonatal period\textsuperscript{37}.

7.4 **Multiple births**

In monozygotic twins, the affected (hypothyroid) twin may not be detected by the initial screening test due to mixing of foetal blood from the euthyroid twin.

**Recommendations**

- Re-testing of thyroid function in same-sex twins at 14 days of life or 2 weeks after first screening.
Explanation
Multiple births have increased in frequency due to progress of fertility treatment in the past four decades\textsuperscript{155}. There is about three-fold increase in incidence of CH in multiple births compared to singletons\textsuperscript{156}. However, concordant rate for CH in these newborns, in particular monozygotic twins, are low\textsuperscript{157}. Therefore, an affected (hypothyroid) twin may have a lower TSH concentration, presumably due to mixture of foetal blood, and fail to be detected by CH screening\textsuperscript{158}. In cases of triplets or higher order of multiple births, the rate of monozygosity is much rarer. To avoid adverse outcomes in affected babies, a strategy to re-screen at least the same-sex twins (which provide the most practical determination of monozygotic twins at the point of screening) at 14 days of life or 2 weeks after first screening may be required. A 14-day interval was decided based on estimation that T4 has a biological half-life of 3.6 days\textsuperscript{112}, and disappearance of T4 is reported to follow the first order kinetic\textsuperscript{158}. This would allow treatment to be started within the first month of life. For dizygotic twins, a recent study suggested that the likelihood for CH in both twins was higher than expected. Therefore, an auxiological follow-up supplemented with hormonal testing if indicated may be useful in this group of patients\textsuperscript{159}.

7.5 Infant of mother with autoimmune thyroid disease (AITD)

Neonates born to mothers with AITD are at risk of developing transient thyroid dysfunction (hyperthyroidism or hypothyroidism) due to pre-natal transplacental passage of maternal thyroid autoantibodies, or antithyroid drugs taken by the mother\textsuperscript{160,161}. Three principal autoantibodies in AITD are anti-thyroperoxidase (ATPo), anti-thyroglobulin (ATG) and TSH receptor antibodies (TRAb). There are two types of TRAbs: TSH-receptor stimulating antibody (TSAb) and TSH-receptor blocking antibody (TBAb). TSAb mimics the action of TSH, stimulates TSH receptor and causes Graves’ hyperthyroidism. TBAb blocks TSH stimulation of the thyroid and causes hypothyroidism. Hence congenital hypothyroidism may occur in neonates born to mothers with antibodies due to AITD, notably the TBAb\textsuperscript{160}. Congenital hypothyroidism can also result from transplacental passage of antithyroid drug taken by the mother with AITD\textsuperscript{161}. While the effect of TBAb persists up to 3-6 months after birth\textsuperscript{89,162}, the effect of anti-thyroid drug lasts a few days to two weeks after birth in the newborn\textsuperscript{161}.

Transient CH caused by maternal TBAb accounts for approximately 1% of all CH cases\textsuperscript{160-165}. It is important to identify these affected newborns and institute treatment early. It is also important to understand that the CH is transient. Maternal TBAb wanes and is cleared from the affected neonates by 3-6 months of age.
**Recommendations**
- All newborns of mothers with AITD or positive for TBAb should have their thyroid function repeated at day 4-6 and at day 10-14 of life even if the initial screen was normal\textsuperscript{166-170}.

- All newborns treated for CH due to maternal AITD should be monitored clinically and biochemically for at least 6 months. The dose of LT4 should be titrated against the thyroid function and tapered accordingly.

**Explanation**
The neonates are at risk of CH if mother with AITD is positive for TRAb or TBAb during pregnancy. The use of anti-thyroid drug in the mother further increases the risk. Hence it is important to repeat the TFT even if the initial screen is normal. As the maternal TRAb or TBAb persist for at least 3-6 months in the affected baby, it is important to monitor the babies while tapering the dose of LT4 to avoid over or under treatment.

Measurement of TRAb or TBAb in all pregnant mothers with AITD may be a reasonable strategy to identify the babies at risk of transient CH for targeted evaluation and treatment.

**7.6 Prolonged neonatal jaundice (PNNJ)**
PNNJ is defined as neonatal jaundice lasting $>$14 days in a term baby or $>$21 days in a preterm baby.

Despite the development of more sensitive tests and improvement in approach strategy, approximately 5-10% of CH cases may still be missed in any screening programme. The reasons could include failure of sample collection, poor samples, failure to recall patients, misinterpretation of results, inappropriate cut-off, delayed TSH rise, and central CH\textsuperscript{171-175}.

Missed cases of CH, particularly the central hypothyroidism which are not diagnosed by the routine TSH-based screening programme may manifest later with PNNJ in the second or third week of life.

**Recommendations**
- All newborns with PNNJ should undergo a detailed clinical evaluation and TFT at presentation to exclude CH.

**Explanation**
Untreated CH is a known cause of PNNJ. Missed cases of CH may be uncovered through PNNJ workup and appropriate treatment should be given to prevent detrimental effects on growth and neurodevelopment.
7.7 Congenital Central Hypothyroidism (CCH)

TSH determination is the most sensitive and effective screening method for congenital primary hypothyroidism. However, this approach will miss CCH where TSH is inappropriately low with a low FT4. Although CCH is rare compared to congenital primary hypothyroidism, delayed diagnosis and treatment result in severe consequences as well. A recent report demonstrated that more than half of CCH have moderately severe hypothyroidism with an initial FT4 <10 pmol/L \(^{176}\). Majority of CCH (74-84\%) is associated with multiple pituitary hormone deficiencies. A high index of suspicion is required to identify babies at risk of CCH and recall patient to re-test FT4 and TSH regardless of the initial screening results.

Newborns with the following features are at risk of CCH:

- Facial mid-line defect e.g. cleft palate or cleft lip, nasal encephalocoele
- Symptoms and signs of pituitary hormones deficiency in a neonate e.g. intractable hypoglycaemia, prolonged cholestatic jaundice, micropenis
- Ocular abnormality e.g. optic nerve hypoplasia

Recommendations

- All newborns at risk of CCH should be recalled for re-test of venous FT4 and TSH at day 4-6, regardless of their initial screening results, and followed up accordingly.

- All newborns with symptoms and signs suggestive of pituitary hormone deficiencies should have FT4 and TSH checked, in addition to other pituitary hormones.

- The mainstay of biochemical diagnosis of CCH is a low FT4 with an inappropriately low or low normal TSH.

- In babies with CCH and concomitant ACTH deficiency, adequate glucocorticoid replacement should precede LT4 treatment to prevent adrenal crisis\(^{177}\).

- The starting dose of LT4 is the same as in primary hypothyroidism.
• Treatment is monitored by measuring FT4 and TSH; FT4 should be kept in the upper half of the age-specific reference range.

• Undertreatment should be suspected when FT4 levels are consistently close to the lower limit of reference range. Overtreatment should be considered when FT4 is consistently around or above the upper limit of the reference range or when there are signs and symptoms of thyrotoxicosis\textsuperscript{178,179}.

**Explanation**

Babies with CCH have low cord blood TSH and would have been deemed normal by TSH-based newborn screening. Babies with CCH will not be recalled for clinical re-evaluation and re-test of thyroid function based on their cord blood TSH level. A post-screening strategy is recommended for all high-risk cases even if they had a normal initial screening result. Untreated CCH can have detrimental effects on the neurodevelopment of the baby.

CCH is frequently associated with other pituitary hormones deficiency. Experience in the North Regional screening programme showed that 84\% of CCH had associated pituitary hormone deficiencies while only 16\% were isolated TSH deficiency\textsuperscript{179}. This was also seen in the Dutch neonatal CH screening programme where 78\% had multiple pituitary hormone deficiency\textsuperscript{180}. Hence newborns showing symptoms and signs of pituitary hormone deficiency should have their thyroid function re-tested. Similarly, newborns with CCH should be tested and monitored for other pituitary hormones deficiency. The pituitary hormone deficiencies may evolve over time\textsuperscript{181}. 
Neonatal screening

- Congenital hypothyroid screening using cord blood collected at birth
- Primary TSH measurement supplemented by FT4 is our preferred strategy. All cord blood is assayed for TSH. In babies with borderline high TSH, free T4 is assayed from the same blood sample.

Interpretation of cord blood TSH and recall of patients

- Cord blood TSH >60 mIU/L (HIGH): Patient is recalled for clinical evaluation and venous TFT to confirm their thyroid status. In patients whose families are disadvantaged or having logistic issues, consideration may be given to start treatment after venous TFT has been taken.

- Cord blood TSH (20-60) mIU/L (BORDERLINE): Cord blood FT4 is measured.
  - Cord FT4 ≤15 pmol/L: Patient is recalled for clinical evaluation and venous TFT.
  - Cord FT4 >15 pmol/L: No further actions are required

- Cord blood TSH <20 mIU/L (NORMAL): No further actions are required

- Patients with cord TSH >60 mIU/L, or (20-40) mIU/L AND cord FT4 ≤15 pmol/L are recalled for clinical evaluation and re-testing of FT4 and TSH at day 4-6.

- In patients where cord blood TSH is not available e.g. home delivery, BBA, rejected blood due to lysis or insufficient blood sample, venous blood should be taken on day 4-6 for measurement of FT4 and TSH
Communication of abnormal neonatal screening results

- There should be an experienced staff in-charge designated to oversee the screening programme, to ensure urgent communication of abnormal results from the laboratory to the assigned clinical staff and to the family and arrange for recall of patient for re-testing of FT4, TSH to confirm the thyroid status.

- If patient has already been discharged, the family should be contacted urgently by phone or through the help of the public health nurse at the Maternal and Child Health Clinic.

Clinical evaluation and re-testing for confirmation of thyroid status

- All newborns with abnormal screening results must be recalled at day 4-6 for a detailed clinical evaluation and re-testing of FT4, TSH for confirmation of thyroid status.

- Clinical evaluation, which include a detailed history and physical examination, should be conducted by a medical officer.

- Evaluation should be focused on eliciting symptoms and signs of congenital hypothyroidism, determining the cause and severity, risk factors and associated congenital abnormalities.

- Venous blood is sampled on the same day for re-testing of FT4, TSH to confirm the thyroid status.

Criteria for diagnosis and decision to initiate treatment

- Day 4-6 venous TSH >40 mIU/L
  Treatment should be started immediately regardless of FT4 concentration.

- Day 4-6 venous TSH 20-40 mIU/L, and
  FT4 < 12 pmo/L, treatment should be started (expert opinion)

  FT4 > 12 pmol/L, FT4, TSH is repeated on day 8-14 If the repeat TSH on Day 8-14 is persistently >20 mIU/L, treatment should be started. However, when taking into account of all the TSH, FT4 levels and TSH is clearly on the downward trend, decision to withhold treatment and re-test may be considered after discussion with the parents and consultation with a paediatric endocrinologist.
• Day 4-6 venous TSH 6-20 mIU/L
Venous TFT is re-checked after 1-2 weeks.

Treatment is indicated if repeat venous FT4 falls below age-specific reference range.

If repeated TSH remains static within 6-20 mIU/L after the age of 21 days in a healthy neonate with a normal FT4, options should be discussed with parents whether to start treatment, or to withhold treatment and to retest 1-2 weeks later to re-evaluate the need for treatment (lack of evidence in favour or against treatment).

• Day 4-6 venous TSH < 6 mIU/L - No further action is required

**Treatment of congenital hypothyroidism**

• LT4 treatment should be started as soon as diagnosis is made.

• An initial dose of LT4 at 10-15 mcg/kg/day (maximum 50 mcg/day) is recommended, the lowest dose for mild disease and higher dose for severe disease.
  › Mild CH (FT4 >10 pmol/L) 10 mcg/kg/day
  › Moderate CH (FT4 5-10 pmol/L) 10 mcg/kg/day
  › Severe CH (FT4 <5 pmol/L) 15 mcg/kg/day
  › Subclinical CH 5-10 mcg/kg/day

• A brand LT4 rather than a generic formulation is recommended especially in the first 3 years of life.

• LT4 should be dispensed in tablet form. LT4 in suspension or syrup form is not recommended. Tablets can be crushed, mixed in small amount of water or milk, and served using a spoon. LT4 should not be served in a milk-bottle.

• Timing of LT4 administration should be consistent every day to ensure compliance. We recommend taking the medication in the morning upon awakening for all ages. LT4 can be taken before, with or after food. However, intake of soy, iron or calcium supplementation within an hour of LT4 administration should be avoided.
Monitoring treatment of congenital hypothyroidism

- Serum FT4 and TSH should be measured before, or at least 4 hours after the last LT4 administration. If timing of blood taking and LT4 administration clashes, LT4 should be delayed until blood has been taken for TFT.

- After initiation of LT4, the first clinical and biochemical follow-up evaluation should be 1-2 weeks later. If the initial dose of LT4 is close to 15 mcg/kg/day or 50 mcg/day, follow-up evaluation should be earlier, within 1 week of treatment initiation.

- Subsequent clinical and biochemical evaluation should be every 2 weeks until TSH normalises.

- Thereafter, the evaluation can be reduced to every 1 to 3 months until the age of 12 months.

- Between the ages of 1 and 3 years, the frequency of evaluations can be lowered to every 2 to 4 months; thereafter, every 3 to 6 months until growth is completed.

- Serum concentration of TSH should be kept within the age-specific reference range and FT4 or TT4 in the upper half of the age-specific reference range. Over-suppression of TSH to <0.5 mIU/L should be avoided.

- Adjustment of LT4 dose should not be based on a single reading of FT4 (or TT4) or TSH. FT4 and TSH should be interpreted together and not in isolation. If FT4 is slightly above the upper limit of normal range with normal TSH, it is safe to continue the same dose of LT4 unless patient manifests symptoms of hyperthyroxinaemia.

- Evaluations should be performed at more frequent intervals if abnormal FT4 or TSH are found or if compliance is questioned.

- After any change in LT4 dose or LT4 formulation (e.g. switching from brand to generic LT4), extra follow-up evaluations should be done 4 to 6 weeks later until FT4 and TSH are normalised.

- The incidence of adverse events during LT4 treatment is very low. However, careful monitoring is recommended to minimise risk.

- Adequate TH replacement throughout childhood is important. Over-treatment or under-treatment when TSH is out of reference range should be avoided.
Re-evaluation of thyroid function

- Re-evaluation of thyroid function is performed on all CH in whom the aetiology and permanence of CH has not been established before initiation of thyroxine replacement i.e thyroid scintigraphy has not been done.

- Re-evaluation is done at or after 3 years of age when myelination in the central nervous system is complete.

- At re-evaluation, thyroxin is stopped for 4 weeks or phased out over 4-6 weeks duration. At the end of this period, venous FT4 and TSH are measured.

- Early re-evaluation may be considered in a CH child who has a GIS and requires a low thyroxine dose of less than 3 mcg/kg/day at the age of 6 months, as he/she is likely to have a transient form of CH. Re-evaluation can be done at or after the age of 6 months.

- Re-evaluation for the need of long term thyroxine therapy may not be required if venous TSH has been persistently >10 mIU/L after 1 year of age despite thyroxine replacement, as this most likely indicate permanent form of CH.

- In patient confirmed to have permanent form of CH at re-evaluation, thyroid ultrasonography should be considered to determine the aetiology of CH if this has not been done previously. Thyroid scintigraphy may also be considered if necessary for definitive aetiological diagnosis.

Outcome of re-evaluation

- If FT4 & TSH are within the normal reference range without thyroxine replacement for 4 weeks, this likely indicates transient CH. Thyroxine replacement is discontinued and thyroid function monitored for the next 6 months. If thyroid function remains normal after 6 months of follow-up, the patient can be discharged.

- If TSH is >10mIU/L without thyroxine replacement for 4-6 weeks, this likely indicates permanent CH. Thyroxine replacement is resumed. The patient continues regular follow-up with periodic clinical and biochemical evaluation to ensure FT4 and TSH are within reference range.
If TSH is <10 mIU/L, but more than upper limit of reference range and FT4 normal, the period without thyroxine replacement is extended for another 3-4 weeks. FT4 & TSH are re-tested at the end of the extended period. Thyroxine replacement is indicated if structural abnormality of the thyroid gland is present, or TSH increases to >10 mIU/L, or FT4 falls to below the reference range for age, or there are symptoms and signs of hypothyroidism.

Monitoring long term outcome

- Neurodevelopment
- Growth and puberty
- Metabolic, cardiovascular and bone health
- Health-related quality of life (QOL)
- Fertility & future pregnancy outcome

Special categories of neonates at risk of congenital hypothyroidism

Sick neonates

- Repeat venous FT4, TSH is recommended about 2 weeks after recovery from illness, irrespective of the initial screening results.

- Treatment of sick neonates with isolated hypothyroxinaemia with LT4 is not recommended.

Preterm infants/low birth weight (LBW)

- In late preterm, 34 to <37 weeks, TFT should be repeated 2 weeks after initial screening.

- In preterm <34 weeks who are not admitted or had only a short stay in the hospital, TFT should be repeated 2 weeks after the initial screening.

- In preterm < 34 weeks who has a prolonged stay in the hospital due to prematurity, TFT should be repeated at 2-weekly interval until discharge and 2 weeks post discharge.

- In LBW (<2.5kg), TFT should be repeated 2 weeks after initial screening. If these babies are admitted to the hospital, TFT should be done at 2-weekly intervals until discharge and 2 weeks post discharge.

- LT4 therapy of isolated hypothyroxinaemia without clear elevation of TSH is not recommended.
Down syndrome (DS)
- TFT should be repeated at 3-4 weeks of life even if the initial screening result is normal.

Multiple births
- Re-testing of thyroid function in same-sex twins at 14 days of life or 2 weeks after first screening.

Infant of mother with autoimmune thyroid disorder (AITD)
- All newborns of mothers with AITD or positive for TBAb should have their thyroid function repeated at day 4-6 and at day 10-14 of life even if the initial screen was normal.
- All newborns treated for CH due to maternal AITD should be monitored clinically and biochemically for at least 6 months. The dose of LT4 should be titrated against the thyroid function and tapered.

Prolonged neonatal jaundice (PNNJ)
- All newborns with PNNJ should undergo a detailed clinical evaluation and thyroid function test at presentation to exclude the diagnosis of congenital hypothyroidism.

Congenital Central Hypothyroidism (CCH)
- All newborns at risk of CCH should be recalled for re-test of venous FT4 and TSH at day 4-6, regardless of their initial screening results, and followed up accordingly.
- All newborns with symptoms and signs suggestive of pituitary hormone deficiencies should have FT4 and TSH checked, in addition to other pituitary hormones.
- The mainstay of biochemical diagnosis is a low FT4 with an inappropriately low or low normal TSH.
- In babies with CCH and concomitant ACTH deficiency, adequate glucocorticoid replacement should precede LT4 treatment to prevent adrenal crisis.
- The starting dose of LT4 is the same as in primary hypothyroidism.
- Treatment is monitored by measuring FT4 and TSH; FT4 should be kept in the upper half of the age-specific reference range.
• Undertreatment should be suspected when FT4 levels are consistently close to the lower limit of reference range. Overtreatment should be considered when FT4 is consistently around or above the upper limit of the reference range or when there are signs and symptoms of thyrotoxicosis.
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<tr>
<th>Abbreviation</th>
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<tr>
<td>AGA</td>
<td>Appropriate for gestational age</td>
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<tr>
<td>AITD</td>
<td>Autoimmune thyroid disease</td>
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<td>BBA</td>
<td>Born before arrival</td>
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<td>CCH</td>
<td>Central congenital hypothyroidism</td>
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<td>CH</td>
<td>Congenital hypothyroidism</td>
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<td>DS</td>
<td>Down syndrome</td>
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<td>FT4</td>
<td>Free thyroxine</td>
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<td>GIS</td>
<td>Gland-in-situ</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>LBW</td>
<td>Low birth weight</td>
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<td>LT4</td>
<td>Levothyroxine</td>
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<td>PNNJ</td>
<td>Prolonged neonatal jaundice</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<td>TFT</td>
<td>Thyroid function test</td>
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