Congenital Hypothyroidism

Congenital Hypothyroidism (CH) is a preventable cause of mental retardation. The worldwide incidence is 1:3000-4000 live births and the estimated incidence in India is 1:2500-2800 live births. Thyroid dysgenesis is the commonest cause accounting for 75-80% of all cases of CH.

Embryology and physiology of the thyroid in the fetus

Thyroid gland originates as a proliferation of endodermal epithelial cells at 3 to 4 weeks of gestation. Synthesis and secretion of thyroxine (T4) and triiodothyronine (T3) starts from 12 weeks of gestation. Thyrotropin-releasing hormone (TRH) and thyroid stimulating hormone (TSH) are detectable by the end of first trimester, but the activity of the hypothalamic-pituitary-thyroid (HPT) axis is low with insufficient production of thyroid hormones until 18 to 20 weeks of gestation. Therefore, the fetus depends on transplacental passage of thyroid hormones during this period. In the second half of gestation, fetal T4 and TSH levels increase progressively.

In the hypothyroid fetus, transplacental passage of maternal thyroid hormones, and increased conversion of T4 to T3 in fetal brain by type 2 deiodinase confer neuroprotection, and near normal cognitive outcomes are possible if maternal thyroid function is normal and postnatal therapy is initiated early. And in contrast, when both maternal and fetal hypothyroidism are present, as in severe iodine deficiency, there is significant neuro-intellectual impairment. Subtle or overt hypothyroidism in the mother during pregnancy also adversely affects the cognitive outcome of the offspring.

Neonatal physiology

As a response to the cold ex-utero environment, there is an early postnatal surge of TSH, rising to 60-80 mU/L within 30 - 60 minutes after delivery, with a rapid fall to about 20 mU/L in first 24 hours, and further decrease to below 10 mU/L by the end of first week. T4 levels also increase to peak levels of approximately 17 µg/dL at 24 -36 hours, with a gradual decline over 4 to 5 weeks. Preterm infants demonstrate a similar but blunted response.
Etiology of CH

CH can be permanent or transient (Table I).

**Table 1 Etiology of CH**

<table>
<thead>
<tr>
<th>1</th>
<th>Permanent hypothyroidism</th>
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<tbody>
<tr>
<td>b</td>
<td>Thyroid dysgenesis (aplasia, hypoplasia or ectopia)</td>
</tr>
<tr>
<td>c</td>
<td>Thyroid hormone biosynthetic defects</td>
</tr>
<tr>
<td>d</td>
<td>Iodine deficiency (endemic cretinism)</td>
</tr>
<tr>
<td>e</td>
<td>Hypothalamic-pituitary hypothyroidism</td>
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</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Transient hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>TSH binding inhibitory immunoglobulins</td>
</tr>
<tr>
<td>b</td>
<td>Exposure to goitrogens (iodides or antithyroid drugs)</td>
</tr>
<tr>
<td>c</td>
<td>Transient hypothyroidinemia of prematurity</td>
</tr>
<tr>
<td>d</td>
<td>Sick euthyroid syndrome</td>
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</tbody>
</table>

**Thyroid dysgenesis** is the commonest cause of permanent CH affecting 1 in 4000 live births. It is usually sporadic with a 2:1 female to male preponderance. Some of the genes proposed as operative in dysgenesis have recently been identified as TITF1, TITF2, PAX8 and TSHR.⁴

**Thyroid hormone synthetic defects** account for 10-15% of all cases. These are inherited as autosomal recessive disorders. The defect can lie in iodide trapping or organification, ioddotyrosine coupling or deiodination, and thyroglobulin synthesis or secretion. The commonest of these is a defect in the thyroid peroxidase (TPO) activity leading to impaired oxidation and organification of iodide to iodine. These disorders usually result in goitrous hypothyroidism. **Iodine deficiency** is responsible for endemic cretinism and hypothyroidism in some regions of India.

**Hypothalamic-pituitary hypothyroidism** is rare and has an estimated incidence of 1 in 50,000. It may be isolated or associated with deficiency of other pituitary hormones and present with hypoglycemia and microphallus.

**Transient hypothyroidism** due to transplacental transfer of TSH binding inhibitory immunoglobulins (TBII) from mothers with autoimmune thyroid disease is seen in 1:50,000 births. Their effect wanes off by 3 to 6 months in the majority, but may last up to 9 months.
Exposure to iodine in sick preterm infants (e.g. application of povidone iodine for skin disinfection (Wolff-Chaikoff effect) or intake of iodine containing expectorants by pregnant mothers can also induce transient hypothyroidism.

**Transient hypothyroxinemia of prematurity** refers to low serum concentration of thyroid hormones in up to 85% of preterm infants in early postnatal life as compared to term infants. This reflects the underdevelopment of the HPT axis. The normal levels of fT4 and TSH in preterm infants are presented in Table 2.5 There has been a concern that transient hypothyroxinemia is associated with adverse neurodevelopmental outcomes and decreased survival in affected infants.

*Sick euthyroid syndrome* reflects suppression of the pituitary’s response to TRH, with inappropriately low TSH concentrations in the context of low T3 and in the more severe cases, low T4 concentrations.

**Table 2.** Reference ranges for serum free T4 (fT4) and TSH in preterm infants

<table>
<thead>
<tr>
<th>Age in weeks</th>
<th>Free T4 (ng/dL)</th>
<th>TSH (mu/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-27</td>
<td>06-2.2</td>
<td>0.2-30.3</td>
</tr>
<tr>
<td>28-30</td>
<td>0.6-3.4</td>
<td>0.2-20.6</td>
</tr>
<tr>
<td>31-33</td>
<td>1.0-3.8</td>
<td>0.7-20.9</td>
</tr>
<tr>
<td>34-36</td>
<td>1.2-4.4</td>
<td>1.2-21.6</td>
</tr>
</tbody>
</table>

**Diagnosis**

*Newborn screening* - Ideally universal newborn screening at 3 to 4 days of age should be done for detecting CH (coupled with screening of other inborn errors of metabolism, wherever it is undertaken). If screening is being done only for CH, cord blood may also be used. Universal newborn screening is currently being done in many parts of the world. Three approaches are being used for screening:

1. Primary TSH, back up T4
2. Primary T4, back up TSH
3. Concomitant T4 and TSH

The advantages and disadvantages of these approaches are presented in Box 1
Box 1: Approaches to screen for congenital hypothyroidism: advantages and disadvantages

1. Primary TSH, back up T4: TSH is measured first, and T4 is measured only if TSH is >20μu/L. This approach is most widely used and cost-effective, but likely to miss central hypothyroidism, thyroid binding globulin (TBG) deficiency and hypothyroxinemia with delayed elevation of TSH.

2. Primary T4, back up TSH: T4 is checked first and if low, TSH is also checked. This is likely to miss milder/subclinical cases of CH in which T4 is initially normal with elevated TSH.

3. Concomitant T4 and TSH: Most sensitive approach but incurs a higher cost. Screening programs use either percentile based cut-offs (e.g., T4 below 10th centile or TSH above 90th centile) or absolute cut-offs such as T4 <6.5 μg/dL and TSH >20μu/L. Among infants with proven CH, TSH is >50 μu/L in 90% and T4 is <6.5 μg/dL in greater than 75% of cases.

Abnormal values on screening should always be confirmed by a venous sample (using age appropriate cut-offs given in Table 3). Most centers initiate treatment after drawing the infants’ sample if TSH >30 μu/L or T4 is low, and the decision to continue or withhold treatment is taken after obtaining the venous blood report. For intermediate screening values of TSH, with normal T4 (if available), the treatment is initiated only after confirmation of diagnosis based on the blood report.

Table 3 Reference ranges for T4, fT4 and TSH in term infants according to postnatal age

<table>
<thead>
<tr>
<th>Age</th>
<th>T4 (μg/dL) mean (range)</th>
<th>fT4 (pg/mL) mean (SD)/ range</th>
<th>TSH (μU/mL) mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>10.8 (6.6-15)</td>
<td>13.8 (3.5)</td>
<td>10.0 (1-20)</td>
</tr>
<tr>
<td>1-3 days</td>
<td>16.5 (11-21.5)</td>
<td>*</td>
<td>5.6 (1-10)</td>
</tr>
<tr>
<td>4-7 days</td>
<td>*</td>
<td>22.3 (3.9)</td>
<td>*</td>
</tr>
<tr>
<td>1-2 weeks</td>
<td>12.7 (8.2-17.2)</td>
<td>*</td>
<td>2.3 (0.5-6.5)</td>
</tr>
<tr>
<td>2-6 weeks</td>
<td>6.5-16.3**</td>
<td>0.9-2.2</td>
<td>1.7-9.1**</td>
</tr>
<tr>
<td>6 weeks to 12 months</td>
<td>11.1 (5.9-13)</td>
<td>*</td>
<td>2.3 (0.5-6.5)</td>
</tr>
</tbody>
</table>

*No data available **data for median/mean not available
In the absence of universal screening, newborns with the following indications should be screened:

1. Family history of CH
2. History of thyroid disease or antithyroid medicine intake in mother
3. Presence of other conditions like Down syndrome, trisomy 18, neural tube defects, congenital heart disease, metabolic disorders, familial autoimmune disorders and Pierre-Robin syndrome, which are associated with higher prevalence of CH

Thyroid function should be tested in any infant with signs and symptoms of hypothyroidism such as postmaturity, macrosomia or wide open posterior fontanel at birth or prolonged jaundice, constipation, poor feeding, hypotonia, hoarse cry, umbilical hernia, macroglossia, or dry edematous skin in infancy. The tests should be performed even in infants who have had a normal newborn screening report.

Once the diagnosis is established, further investigations to determine the etiology should be done. A nuclear scan using sodium pertechnate ($^{99m}$Tc) is especially useful in diagnosing true athyrosis or ectopy as well as goitrous hypothyroidism due to dyshormonogenesis. However, since the scan can be done only before initiating treatment, one should not withhold therapy if it is not possible to get it performed immediately. A list of diagnostic studies useful in infants with congenital hypothyroidism is presented in Table 4 and an algorithmic approach to investigation in Figure 1.
Figure 1 Approach to a newborn infant with positive screening test for CH

Positive Screening test on filter paper sample

Serum T4/ Free T4, TSH

Normal

Abnormal

↓ Thyroid scan

Normal uptake

Absent uptake

↓ Ultrasound

Normal gland

No Thyroid tissue

↓ Tg Measurement

Normal

Absent

↓ TBII measurement *

Positive

Negative

↓ Transient

CH

TH synthetic defect or

Tg synthetic defect

TSH receptor defect or TH biosynthetic defect

Transient

Thyroid agenesis

Ectopic

TBII = TSH binding inhibitory immunoglobulin (*not routinely available)
Tg = thymoglobulin, TH = thyroid hormone
Adapted from Fisher DA. Management of congenital hypothyroidism. J Clin Endocrinol Metab 1991;72:585-8
Table 4 Diagnostic studies for evaluation of CH

1. Imaging Studies: will determine location and size of thyroid gland
   a. Scintigraphy (\(^{99m}\text{Tc}\) or \(^{123}\text{I}\))
   b. Sonography

2. Function Studies
   a. \(^{123}\text{I}\) uptake
   b. Serum thyroglobulin

3. Suspected inborn error of T4 synthesis
   a. \(^{123}\text{I}\) uptake and perchlorate discharge

4. Suspected autoimmune thyroid disease
   a. Maternal and neonatal serum TBII measurement (not routinely available)

5. Suspected iodine exposure or deficiency
   a. Urinary iodine measurement

6. Ancillary test to determine severity of fetal hypothyroidism
   a. Radiograph of knee for skeletal maturation

When should we ask for free T4 levels?

In most situations, T4 (total) levels are sufficient for diagnosis of hypothyroidism and monitoring treatment, but free T4 can be obtained as a more robust marker of the bioavailable T4, when readily accessible. When availability or cost is a constraint, free T4 should be definitely estimated in following situations:\(^8,13\)

1. In premature or sick newborns, T4 (total) values may be low because of abnormal protein binding or low levels of thyroxine binding globulin (TBG) due to immaturity of liver function, proteinuria or undernutrition. Therefore, free T4 values provide a better estimate of true thyroid function.

2. A case of low T4 with normal TSH. If free T4 is normal, it can be a case of congenital partial (prevalence 1:4000 to 12000 newborns) or complete (prevalence 1:15000 newborns) TBG deficiency. TBG levels should be evaluated to confirm this but this test is not available routinely. If free T4 is also low along with low T4 with normal TSH, central hypothyroidism should be suspected.

3. During monitoring for adequacy of treatment, we usually monitor T4 (total) level. This assumes a normal TBG level. This can be confirmed by measuring free T4 or TBG levels once at the time of the first post-treatment T4 measurement.
Treatment of CH

Term as well as preterm infants with low T4 and elevated TSH should be started on L-thyroxine as soon as the diagnosis is made. The initial dose of L-thyroxine should be 10-15 µg/kg/day with the aim to normalize the T4 level at the earliest.

Those infants with severe hypothyroidism (very low T4, very high TSH and absence of distal femoral and proximal tibial epiphyses on radiograph of knee) should be started with the highest dose of 15µg/ kg/ day.14

Monitoring of therapy:

- T4 should be kept in the upper half of normal range (10 to 16 µg/dL) or free T4 in the 1.4 to 2.3 ng/dL range with the TSH suppressed in the normal range.
- Check T4 and TSH levels according to the following schedule:
  - 0 to 6 months: every 6 weeks
  - 6 months to 3 years: every 3 months
  - Beyond 3 years: every 6 monthly
  - 6 to 8 weeks after any dosage change.
- Monitor growth and development of the infant.
- Avoid over treatment as it can lead to premature fusion of cranial sutures, acceleration of skeletal maturation and problems with temperament and behavior.

Special situations

1. Asymptomatic hyperthyrotropinemia (Elevated TSH, normal T4)
   - Can be transient or permanent
   - Perinatal iodine exposure is an important cause of transient elevation of TSH in neonatal period.
   - Other causes include defects in biological activity of TSH or TSH receptor, mild thyroid hormone biosynthesis defect, subtle developmental defects or disturbance in the negative feedback control of TSH.
   - There is controversy regarding need for treatment
   - Persistently elevated TSH> 10 µU/ml is generally treated. However, in the presence of free T4 levels in upper half of normal range, expectant management can be followed with repetition of tests after 2 weeks.
   - In case treatment is started, it should be continued till 3 years of age, with monitoring of thyroid function as detailed above. If TSH and T4 have always been within normal limits with no need for escalation of dose during the first 3 years, thyroid function should be re-evaluated after withholding thyroxine for a period of 6 weeks.14

2. Isolated hypothyroxinemia (Low T4 and normal TSH levels)
   - This clinical situation is commonly seen in preterm infants due to immaturity of HPT axis and is labeled as ‘Transient hypothyroxinemia of prematurity’. As of now, there is insufficient evidence that early treatment with thyroid hormone leads to
improved outcomes.

- Central (hypothalamic/ pituitary) hypothyroidism (Incidence 1 in 1,00,000) is also characterized by low T4. TSH may be low or normal. In term infants, with low total as well as free T4, this diagnosis should be considered, especially in presence of midline facial abnormalities, hypoglycemia, microphallus, or visual abnormalities. The infant should undergo testing for other pituitary hormones and MR imaging of hypothalamus and pituitary.
- TBG deficiency (rare) can also present with low T4 and normal TSH. Free T4 is normal and no treatment is required.

3. Transient Hypothyroidism

- The causes are listed in Table 1.
- Infants with transient hypothyroidism due to maternal goitrogenic drugs need not be treated unless low T4 and elevated TSH values persist beyond 2 weeks. Therapy can be discontinued after 8-12 weeks. Intake of antithyroid drugs can be continued by the hyperthyroid mothers during breast feeding because concentration of these drugs is very low in breast milk.
- In infants born to mothers with autoimmune thyroiditis, treatment should be started if T4 is low. If presence of TBII is documented in the infant, treatment can be discontinued at 3-6 months. However, when TBII estimation is not available, treatment should be continued till the age of 3 years, when T4 and TSH can be tested after withholding thyroxine for 6 weeks.

The management has been summarized in Panel 1.

Table 5 provide research priorities in CH.

Outcome

The best outcome occurs with L-thyroxine therapy started by 2 weeks of age at 9.5 µg/kg or more per day, compared with lower doses or later start of therapy. Residual defects can include impaired visuospatial processing and selective memory and sensorimotor defects. More than 80% of infants given replacement therapy before three months of age have an IQ greater than 85 but may show signs of minimal brain damage, including impairment of arithmetic ability, speech, or fine motor coordination in later life. When treatment is started between 3-6 months, the mean IQ is 71 and when delayed to beyond 6 months, the mean IQ drops to 54.
References


4. Macchia P. Recent advances in understanding the molecular basis of primary congenital hypothyroidism. Mol Med Today 2000;6:36–42.


14. LaFranchi SH, Austin J. How should we be treating children with congenital hypothyroidism? J Pediatr Endocrinol Metab 2007; 20:559-78.


<table>
<thead>
<tr>
<th>Research question</th>
<th>Subjects</th>
<th>Study design</th>
<th>Intervention</th>
<th>Outcomes to be measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the effect of transient hypothyroxinemia of prematurity on neuro-intellectual outcome and mortality at 1 year of age</td>
<td>Preterm newborns, birth weight &lt; 1500 g</td>
<td>Cohort study</td>
<td>None</td>
<td>Development quotient</td>
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<td></td>
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<td>Presence/ absence of neurological disability</td>
</tr>
<tr>
<td>What is the effect of maternal subtle hypothyroidism in pregnancy on gestation, birth weight and neuro-developmental outcome in offspring?</td>
<td>Women found to have elevated TSH and normal T4 on screening within first 20 weeks of gestation, and their offspring</td>
<td>Cohort study</td>
<td>None</td>
<td>Birth weight</td>
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<td>Neuro-development at 2 years of age</td>
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