Hypothyroidism in Pregnancy

Physiologic changes during pregnancy

Early in pregnancy estrogen promotes production of a more highly sialylated T₄-binding globulin isoform that is less rapidly degraded (reduced hepatic clearance), resulting in an increased serum T₄-binding globulin and T₄ concentrations. The test results that change significantly are those that are influenced by serum TBG concentration. These include total thyroxine (TT₄), total triiodothyronine (TT₃), and resin triiodothyronine uptake (RT₃U).

Although a transient decrease in serum free T₄, followed by a rise in TSH may occur, this is usually not seen with routine thyroid testing. A high circulating HCG level in the first trimester leads to HCG cross reactivity with the TSH receptor, prompting a temporary increase in a T₄ and partial suppression of TSH.

The final physiologic change results from placental deiodination of maternal T₄, which increases T₄ turnover. In addition, there is increased renal clearance of iodide. This alteration is associated with a noticeable increase in thyroid gland size in ~15% of women.

Changes in Thyroid Function Test Results in Normal Pregnancy and in Thyroid Disease

<table>
<thead>
<tr>
<th>Maternal Status</th>
<th>TSH</th>
<th>FT₄</th>
<th>FTI</th>
<th>TT₄</th>
<th>TT₃</th>
<th>RT₃U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Increase</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Decrease</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase or no change</td>
<td>Increase</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Increase</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease or no change</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

Abbreviations: TSH, thyroid-stimulating hormone; FT₄, free thyroxine; FTI, free thyroxine index; TT₄, total thyroxine; TT₃, total triiodothyronine; RT₃U, resin T3 uptake.

Fetal thyroid development begins at 10-12 weeks gestation and is not complete until delivery. T₄ is not secreted until 18-20 weeks gestation.

TSH does not cross the placenta and only small amounts of T₄ and T₃ cross the placenta. TRH, iodine, and TSH receptor immunoglobulins do cross the placenta as do the thioamides, propylthiouracil (PTU) and methimazole.

T₄ is critical for many aspects of brain development including neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis, and neurotransmitter regulation.

- Studies in partially thyroidectomized (parathyroid spared) Sprague-Dawley rats demonstrate decreased levels of glial fibrillary acidic protein, suggesting delayed astrocytic differentiation, which were only apparent after onset of fetal T₄ secretion.
- Studies in hypothyroid induced Sprague Dawley rats have also demonstrated decreased expression of synaptotagmin related gene 1 protein, which is involved in the regulation of neurotransmission. Upon in vitro exposure for 24 hours to T₄, cerebellar granule cells srg1 mRNA was rapidly upregulated.

Impact of maternal hypothyroïdism and/or hypothyroxinemia

The incidence of maternal hypothyroidism in the U.S. during pregnancy is ~2.5%. The prevalence of subclinical hypothyroidism in the US adult population is ~4 to 8.5% in those without known thyroid disease.

The severity, timing of onset and duration, as well as the postnatal management all influence fetal and neonatal brain development.

The most severely affected infants have neurologic cretinism, manifest as mental retardation (IQ ~ 29) and impaired gait and motor function. These abnormalities have been associated with maternal T₄ but not T₃ levels during pregnancy. Untreated hypothyroidism is associated with several complications including preeclampsia and low birth weight as well as abruptio placetae and an increased risk of spontaneous abortion and perinatal mortality. The etiology of low birth weight was medically indicated preterm delivery, Preeclampsia, or placental abruption.
In 1999, Klein retrospectively screened 25,000 mothers for hypothyroidism in New England. TSH concentrations ≥ 97.7 percentile was considered to indicate hypothyroidism. The women formed three groups: 14 women with previously diagnosed hypothyroidism who had been treated before and throughout pregnancy; 48 women whose hypothyroidism was not treated during pregnancy; and 124 matched controls whose TSH was < 97.7 percentile. Compared with children of treated mothers (IQ 111±3.3), children of untreated mothers had a lower IQ (100±2.2, p = 0.04) when measured at 8 years of age.

In 1999, Pop et al., prospectively assessed mental and psychomotor development in 125 (63 cases, 62 controls) 10-month old infants living in The Netherlands, an iodine sufficient country. They found that if the mother’s free-T4 was in the lowest 10th percentile at 12 weeks gestation, the infants had an increased risk of delayed psychomotor development (RR 5.8). Two years later, 115 subjects were available for followup (57 cases, 58 controls).

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>One year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental, mean (SD)</td>
<td>98 (15)</td>
<td>106 (14)</td>
<td>0.02</td>
<td>4-12</td>
</tr>
<tr>
<td>Motor, mean (SD)</td>
<td>92 (16)</td>
<td>102 (16)</td>
<td>0.005</td>
<td>6-16</td>
</tr>
<tr>
<td>Two years</td>
<td></td>
<td></td>
<td></td>
<td></td>
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Differences on the Bayley mental (MDI) and motor (PDI) subscales - assessed both at 1 and 2 years - of 57 children of mothers with hypothyroxinaemia (an fT4 ≤ 10th percentile, cases) during early gestation and 58 children of mothers with an fT4 between the 50th and 90th percentiles controls (t-test, two tailed). *Clinical Endocrinology, 59*, p. 285.

**Diagnosis**

- Free T₄ is the preferred test because it is relative maternal hypothyroxinemia, not a mild TSH elevation, which puts the fetus at risk.
- If the FT₄ is not available, the free thyroxine index (FTI) can be calculated where FTI = RT₃U * TT₄. In general, measurement of FT₃ is usually only pursued in patients with thyrotoxicosis with a suppressed TSH and normal FT₄. Elevated FT₃ indicates T₃ toxicosis, which may occur before excessive FT₄ production develops.

**Treatment**

The World Health Organization recommends 200 µg/day iodine intake for pregnant and lactating women.

Smallridge and Ladenson (2001) reviewed four case series in which serum TSH increased by 58%. In their analysis, the mean L-thyroxine dose increased from 117 µg to 150 µg. Lazarus (Thyroid, 2002) recommended an increase on the order of 50 to 100 µg LT₄/day.

Alexander, NEJM 2004, identified 19 women with primary hypothyroidism from the outpatient endocrine clinics at Brigham and Women’s Hospital in Boston, MA. They sought to delineate the timing and pattern of increased thyroid hormone requirement during pregnancy in order to determine appropriate recommendations for preventing first trimester hypothyroidism. Measurements were made every two weeks in the first trimester and monthly thereafter. Six women were initially maintained at a greater degree of suppression due to a history of thyroid cancer. Subjects were instructed not to ingest vitamins or products containing calcium, iron, or soy within four hours of their Levothyroxine. Serum thyrotropin levels increased during the first 10 weeks of gestation prompting an increase in the LT₄ dose in 85% of the group. The dose of LT₄ was quickly increased from 6 to 16 weeks and then remained the same.
At 10 weeks gestation, the dose of LT4 has increased 29 ± 25% (p<0.001). At 20 weeks, the increase relative to baseline was 48 % (p < 0.001) and the dose remained stable thereafter. Based on these observations, it is suggested that women under treatment for hypothyroidism increase their dose of LT4 by 30% beginning the week pregnancy is confirmed.

It takes approximately 4 weeks for thyroxine therapy to alter TSH levels. Therefore, Levothyroxine (LT4) therapy should be adjusted at 4 weeks intervals until TSH levels are stable.

The incidence of congenital hypothyroidism is 1 per 4000 newborns. All 50 states offer screening for congenital hypothyroidism. If identified with the first few weeks of life, near normal growth and intelligence can be expected.

References


6. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004 Jan 14; 291(2):228-38.


Additional Reading


