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Hypothyroidism in Pregnancy

Physiologic changes during pregnancy

Early in pregnancy estrogen promotes production of a more highly sialylated T_4-binding globulin isoform that is less rapidly degraded (reduced hepatic clearance), resulting in an increased serum T_4-binding globulin and T_4 concentrations. The test results that change significantly are those that are influenced by serum TBG concentration. These include total thyroxine (TT_4), total triiodothyronine (TT_3), and resin triiodothyronine uptake (RT_3U).

Although a transient decrease in serum free T_4, 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 T_4 and partial suppression of TSH.

The final physiologic change results from placental deiodination of maternal T_4, which increases T_4 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
ACOG Practice Bulletin 37. Thyroid Disease in Pregnancy, August 2002

Maternal Status	TSH	FT_4	FTI	TT_4	TT_3	RT_3U
Pregnancy	No change	No change	No change	Increase	Increase	Decrease
Hyperthyroidism	Decrease	Increase	Increase	Increase	Increase or no change	Increase
Hypothyroidism	Increase	Decrease	Decrease	Decrease	Decrease or no change	Decrease

Abbreviations: TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FTI, free thyroxine index; TT_4, total thyroxine; TT_3, total triiodothyronine; RT_3U, resin T3 uptake.

Fetal thyroid development begins at 10-12 weeks gestation and is not complete until delivery. T_4 is not secreted until 18-20 weeks gestation.

TSH does not cross the placenta and only small amounts of T_4 and T_3 cross the placenta. TRH, iodine, and TSH receptor immunoglobulins do cross the placenta as do the thioamides, propylthiouracil (PTU) and methimazole.

T_4 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 T_4 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 T_4, cerebellar granule cells srg1 mRNA was rapidly upregulated.

Impact of maternal hypothyroidism 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 T_4 but not T_3 levels during pregnancy. Untreated hypothyroidism is associated with several complications including preeclampsia and low birth weight as well as abruptio placentae 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.

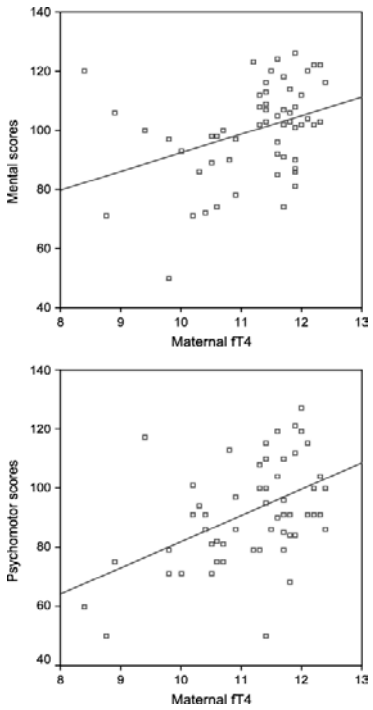
In 1999, Klein retrospectively screened 25,000 mothers for hypothyroidism in New England. TSH concentrations ≥ 97.7 percentile was considered to indicate hypothyroidism. The women formed three groups: 14 women with previously diagnosed hypothyroidism who had been treated before and throughout pregnancy; 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-T_4 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).

	Cases	Controls	*P*	95% CI
One year				
Mental, mean (SD)	95 (15)	105 (14)	0·004	4-16
Motor, mean (SD)	91 (15)	99 (14)	0·02	3-12
Two years				
Mental, mean (SD)	98 (15)	106 (14)	0·02	4-12
Motor, mean (SD)	92 (16)	102 (16)	0·005	6-16

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.

Scatter diagram of a linear regression of maternal fT4 concentrations of the cases (fT4 at 12 weeks' gestation below the 10th percentile, *n*= 57) with, at 2 years of age, mental (top, R^2= 0·13, *P*= 0·006) and psychomotor (bottom, R^2= 0·23, *P*= 0·001) scores of the Bayley scale. *Clinical Endocrinology*, **59**, p. 286.



Diagnosis

- Free T_4 is the preferred test because it is relative maternal hypothyroxinemia, not a mild TSH elevation, which puts the fetus at risk.
- If the FT_4 is not available, the free thyroxine index (FTI) can be calculated where FTI = RT_3U * TT_4. In general, measurement of FT_3 is usually only pursued in patients with thyrotoxicosis with a suppressed TSH and normal FT_4. Elevated FT_3 indicates T_3 toxicosis, which may occur before excessive FT_4 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.

Table 2. Serum Values before and during Gestation in All Women Who Required an Increase in the Dose of Levothyroxine during Gestation.*

Variable	Week of Gestation					P Value by ANOVA	P Value by Newman–Keuls Test					
	Before Pregnancy	10	20	30	38		Before Pregnancy vs. 10 wk	Before Pregnancy vs. 20 wk	Before Pregnancy vs. 38 wk	10 wk vs. 20 wk	20 wk vs. 38 wk	30 wk vs. 38 wk
Thyrotropin (μU/ml)	1.0±1.14	4.2±3.8	2.3±3.2	1.3±1.5	1.0±0.9	0.002	<0.01	0.29	0.99	0.04	0.28	0.93
Free thyroxine index	8.8±1.2	7.8±1.8	8.9±1.5	8.5±1.7	8.5±1.8	0.33	NA	NA	NA	NA	NA	NA
Thyroid hormone–binding ratio	1.0±0.1	0.8±0.1	0.7±0.05	0.6±0.06	0.6±0.1	<0.001	<0.001	<0.001	<0.001	<0.001	0.79	0.99
Thyroxine dose (fraction of dose before pregnancy)	1.00±0	1.29±0.25	1.48±0.18	1.48±0.15	1.47±0.17	<0.001	<0.001	<0.001	<0.001	<0.001	0.99	0.99
Estradiol (pg/ml)	55±24	1100±400	7000±2800	13,500±3500	20,400±4200	<0.001	0.91	<0.001	<0.001	<0.001	<0.001	<0.001

* Plus–minus values are means ±SD. To convert the values for estradiol to picomoles per liter, multiply by 3.67. ANOVA denotes analysis of variance, and NA not applicable.

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.

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