

Hypothyroidism: Should we screen all pregnant women?

What are the practical implications of recent studies linking maternal thyroid deficiency with impaired growth, adverse neurologic outcomes, and fetal death?

Emerging research indicates that thyroid hormones play a key role in fetal brain development, and asymptomatic hypothyroidism during pregnancy may have an adverse effect on fetal growth and neurologic development. Findings published in the past year call our attention to the importance of identifying and adequately treating thyroid-deficient gravidas:

- Maternal free thyroxine (FT4) concentration below the 10th percentile at 12 weeks is associated with significant impairment of psychomotor development at ages 1 and 2 years.¹
- The average serum thyroid-stimulating hormone (TSH) and FT4 levels of neonates born to hypothyroid mothers were significantly

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higher than those of controls; birth weight and head circumference were significantly lower.²

But given the paucity of data on *how* maternal hypothyroidism affects the offspring, is universal screening justified? We review the evidence to date, present the current positions of 3 organizations, and offer recommendations for current clinical practice.

Maternal thyroid status is important throughout gestation

The fetal thyroid gland begins to develop at 3 weeks' gestation; it concentrates iodine and synthesizes thyroid hormone after 10 to 12 weeks.

Prior to this, the mother provides the thyroid hormones through placental diffusion (see "How thyroid needs change during pregnancy," page 41). Indeed, thyroid hormones

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CLINICAL RECOMMENDATIONS

- In the general population, thyroid function testing—specifically, thyroid-stimulating hormone (TSH) and free thyroxine (FT4) studies—prior to conception or in early pregnancy is reasonable, but the decision should be left to the individual patient and her physician.
- TSH and FT4 testing should be performed prior to conception and during pregnancy in women with a family history of thyroid disease, symptoms of thyroid disease, or an immune disorder.
- For women with a personal history of hypothyroidism who are taking thyroxine (T4) replacement, serum TSH should be closely monitored in early pregnancy. Most of these patients will become hypothyroid as detected by a rise in TSH unless the T4 dose is increased in early pregnancy.
- For pregnant women found to be hypothyroid, close monitoring (4 to 6 week intervals) of TSH and FT4 throughout pregnancy and careful adjustment of the thyroid supplementation dosage are warranted.

have been detected in human coelomic and amniotic fluids as early as 8 weeks' gestation, before the fetal thyroid starts to function.³

New perspective on role of maternal thyroid function. It was previously believed that the mother's thyroid hormone supply to the fetus was irrelevant after 10 to 12 weeks. However, Vulsma et al⁴ demonstrated that substantial amounts of thyroxine (T₄) are transferred from mother to fetus during late gestation. They discovered T₄ in the cord blood of fetuses at term who were unable to synthesize T₄ due to organification defects or thyroid agenesis. The T₄ in these cases (noted at concentrations 25% to 50% of normal) was obviously of maternal origin.

Thyroid hormones: Important to brain differentiation and development

In the mammalian embryo, thyroid hormones appear to regulate processes of neuronal proliferation, migration, synaptogenesis and myelination, though the precise mechanism is not fully understood.

Unlike T₄, triiodothyronine (T₃, the most potent thyroid hormone) does not readily penetrate the brain. Indeed, most brain T₃ is produced locally from T₄, after which it binds to nuclear thyroid hormone receptors. These in turn bind to specific DNA sequences in the regulatory region of target genes.⁵ A sufficient level of such receptors has been observed in the human fetus as early as 9 weeks' gestation.

Information comes mostly from animal models, mainly rats. We must thus remain aware that the transfer of thyroid hormones from mother to embryo or fetus may differ between species,⁶ as may the stages of brain development before and after birth.

Hypothyroidism during pregnancy

The frequency of thyroid deficiency in pregnancy varies from 0.19% in Japan⁷ to 2.2% in Belgium⁸ and 2.5% in the United States.⁹

Hypothyroidism in pregnancy may be due to preexisting illness or a disease that evolves

during pregnancy; in developed nations, the most common causes are Hashimoto's thyroiditis, subacute thyroiditis, and surgical or radioactive ablation of the thyroid gland.

The hypothyroid state may be subclinical and can remain undiagnosed throughout pregnancy. The clinical manifestations of hypothyroidism (fatigue, sensitivity to cold, muscle irritability, cramps, constipation, paresthesia of the distal portion of the extremities, dry skin, and hair loss) may be masked in gestation as symptoms of pregnancy. Gestational hypothyroidism can be classified as overt (low FT₄ values and elevated TSH) or subclinical (normal FT₄ values and elevated TSH).

The IQ scores of children of hypothyroid women averaged 4 points lower than those of controls at age 7 to 9 years.

Increased rates of fetal death have also been associated with subclinical disorder (see "The importance of adequate supplementation: 2 case studies," page 42).¹⁰

Monitoring thyroid hormone levels in hypothyroid women is performed several times during gestation (every 4 to 6 weeks), and the dosage of T₄ supplementation adjusted as needed. Mandel et al, who studied women with primary hypothyroidism, noted that the replacement dosage had to be increased by 45% during pregnancy.¹¹ This trend was apparent in the first trimester and persisted throughout gestation.

How does maternal thyroid status affect fetal brain development?

Data on the impact of maternal hypothyroidism on the offspring's mental development come from interventional experimental studies in animals, and, in humans, from observational studies only.

Animal studies show permanent cortical changes. Hypothyroidism in rats causes a reduction in brain size of the newborn pups

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How thyroid hormone needs change during pregnancy

Thyroid hormone requirement increases during pregnancy in normal women, to provide for the added maternal and fetal needs. Thyroxine (T4) requirement also may grow as a result of placental degradation and increased maternal T4 clearance.²⁰

Thyroid hormone turnover is altered during pregnancy, mainly in association with:

- lowered iodide availability to the maternal thyroid gland,
- increased serum thyroid-binding globulin (TBG) concentration, and
- increased production of thyroid-stimulating factors by the placenta.

■ **Maternal serum inorganic iodide levels decrease during pregnancy,** possibly due to increased renal clearance of iodide—which stems from increased glomerular filtration rate, and transplacental transfer of iodide and iodothyronines.^{8,21} The reduced circulating concentration of iodide leads to decreased availability of iodide to the thyroid gland, and results in a 10% to 20% increase of thyroid volume.²¹ This iodide loss has no clinical importance where iodine

intake is sufficient, but may lead to hypothyroidism and goiter in regions of overt iodine deficiency.

■ **The increase in the TBG serum concentration in pregnancy** results from estrogen-induced increased synthesis and reduced hepatic clearance of TBG.

Serum TBG starts to rise after conception and reaches a plateau at midgestation, leading to an increase in total T4 and total triiodothyronine (T3) levels. In addition, the placenta produces human chorionic gonadotropin (hCG), which has thyroid-stimulating hormone (TSH)-like bioactivity and stimulates T4 production by the thyroid gland. Placental production of hCG is maximal during the first trimester.

Thus, total T4 and total T3 levels rise during the first trimester to a peak in midgestation. However, only a small amount of these hormones is unbound: The increase in free T4 during this trimester is mild, and coincides with a mild transient decrease in TSH levels that subsequently return to normal.

Most pregnant women are euthyroid by laboratory evaluation, and their TSH, free T4, and free T3 levels remain within normal values.

and a lower total body mass of the embryos.¹²

Lavado-Autric et al¹³ recently reported that subtle T4 insufficiency in the pregnant rat disrupts migration of neurons in the fetal cortex and hippocampus, leading to the presence of neurons in aberrant locations in the adult offspring's brain and "blurring" of cortical layers. These alterations in cortical cytoarchitecture seem to be permanent, not simply a reflection of delayed maturation.

Recent human studies point to neurologic impairment. It is well recognized that severe iodine deficiency during pregnancy may be associated with impaired psycho-neuro-intellectual outcome in progeny. However, since thyroid hormone deficiency can occur in both mother and fetus, it is difficult to determine whether any mental retardation is caused by maternal or fetal hypothyroidism, or both.

■ **Elevated maternal TSH associated with lower child IQ scores.** Man and Jones¹⁴ first suggested in 1969 that mild maternal hypothyroidism with no iodine deficiency was associated with lower infant IQ scores.

More recently, Haddow et al¹⁵ also found that maternal hypothyroxinemia is associated with adverse neurologic outcome of the offspring. They measured TSH in stored serum samples collected from 25,216 pregnant women. The children of 62 women who had elevated TSH (above the 98th percentile) in combination with low T4 levels were compared to 124 children of matched control mothers.

The children of hypothyroid women performed slightly worse than controls in a battery of 15 neuropsychological tests at the age of 7 to 9 years; their full-scale IQ averaged 4 points lower ($P = .06$).

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The importance of adequate supplementation: 2 case studies

The following cases underscore the importance of:

- knowledge of maternal thyroid status during periconception,
- thyroid hormone supplementation for subclinical hypothyroidism, and
- close follow-up and appropriate adjustment of replacement therapy throughout pregnancy.

Case 1

Elevated TSH discovered after successive pregnancy losses

A woman suffered 2 consecutive pregnancy losses. Subsequent work-up revealed subclinical hypothyroidism: Her thyroid-stimulating hormone (TSH) value was moderately elevated and free thyroxine (FT4) was normal. Thyroid hormone supplementation was initiated.

Four months later the patient conceived spontaneously. Levothyroxine therapy in the prepregnant dosage was continued. The mother's general physician monitored her levels during gestation.

TSH value was normal at 5 weeks but elevated again at 9 weeks. The dosage of thyroid hormone supplementation was increased and the TSH value returned to normal—and remained so in all subsequent studies, every 4 to 6 weeks until labor.

The child was born at 40 weeks' gestation, with a birth weight of 3,680 g, a head circumference of 36 cm, and normal neonatal thyroid functions. Presently 7 years old, he is healthy and well developed.

Case 2

The perils of unmonitored supplementation

A year after her thyroid function was found to be normal, a woman became pregnant. At the 5th gestational week, fatigue and constipation prompted reexamination of her thyroid function. TSH values were elevated; FT4 was borderline low.

According to her endocrinologist she was given levothyroxine 100 µg daily throughout pregnancy, but no follow-up was conducted. At 39 weeks' gestation the patient delivered a male newborn weighing 2,890 g with a head circumference of 33.7 cm. Neonatal thyroid function was:

- at 52 hours of age, TSH = 14.3 µIU/mL, FT4 = 37.4 pmol/L;
- at 132 hours of age, TSH = 8.0 µIU/mL, FT4 = 31.5 pmol/L.

Spontaneous normalization of the pituitary-thyroid axis was evident at age 17 days. The child, now 9 years old, displays problems with fine motor coordination and mild learning impairment.

Thyroid supplementation not associated with improved IQ. Of the 62 women with overt disease, only 14 were treated for hypothyroidism during pregnancy. The full-scale IQ score of the children born to untreated women averaged 7 points lower ($P = .005$) than that of matched controls. Interestingly, there was no significant difference in mean IQ between the children born to treated and untreated hypothyroid mothers, suggesting therapy had no significant protective effect on IQ.

However, since the 14 treated mothers still had high TSH levels, it is possible that they actually received suboptimal treatment.

▪ **First trimester hypothyroidism linked to impaired psychomotor development.** A 2003 study by Pop et al¹ investigated the relationship between maternal hypothyroxinemia in the first trimester and neurodevelopment of the offspring. They showed that low maternal FT4 (below the 10th percentile) with normal TSH at 12 weeks' gestation was associated with significant impairment of the child's psychomotor development at 1 and 2 years of age.

However, children whose mothers' FT4 concentrations increased later in pregnancy (24 and 32 weeks' gestation) did not demonstrate significant delay of mental and motor function at age 1 or 2.

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This study is limited by small numbers in the subgroups (63 cases and 62 controls at 1 year; 57 cases and 58 controls at 2 years). Further research is required to evaluate results.

▪ **Alterations in the pituitary-thyroid axis noted in the early neonatal period.** Recently, we prospectively compared thyroid function in 2 groups of full-term newborns: 259 infants born to 250 hypothyroid mothers who received thyroid replacement therapy during pregnancy, and 139 healthy newborns of women who had at least 2 normal thyroid function tests during their pregnancy.² Maternal thyroid function tests were assessed 2.3 ± 0.7 (mean \pm standard deviation) times during pregnancy.

The neonates' average serum TSH and FT4 levels, measured 25 to 120 hours after birth, were significantly higher among a substantial subset of the intervention-group newborns (44.4%, $P < .001$) than among control-group newborns. Serum FT4 correlated positively with TSH in controls but not in study newborns, suggesting autonomous hyperfunction of the thyroid gland in the latter group.

Birth weight (study, $3,295 \pm 446$ g versus control, $3,454 \pm 413$ g; $P < .001$) and head circumference (study, 34.6 ± 1.4 cm versus control, 35.1 ± 1.0 cm; $P < .001$) were significantly lower in the study group.

We assume that the impaired intrauterine growth and unduly elevated serum TSH and FT4 values observed in the study newborns might reflect insufficient hormone replacement of their mothers during pregnancy.

Official guidelines are unclear

Considering the adverse effects that maternal hypothyroidism, even subclinical, can have on the offspring, the question arises: Is universal periconceptional screening for thyroid dysfunction appropriate? The current recommendations on this subject are unclear: **The Endocrine Society** in 1999 called for a cost-effective screening program for hypothyroidism in all women before conception or in early pregnancy.¹⁶

The American Association of Clinical Endocrinologists recommended in 2002 that routine TSH measurement be performed before pregnancy or during the first trimester in all women.¹⁷

The American College of Obstetricians and Gynecologists, in contrast, stated in 2002 that data are insufficient to warrant routine screening of asymptomatic pregnant women; thyroid function tests should be performed only in gravidas with symptoms or a personal history of thyroid disease.¹⁸

Why routine screening is not yet justified

In view of the findings of adverse events associated with maternal hypothyroidism, a universal screening program appears warranted for timely initiation of therapy. However, data on the efficacy of T4 replacement in averting such effects is insufficient. Thus, it is premature to implement routine screening for thyroid function of all women contemplating pregnancy or early in gestation.

Well-designed clinical trials are needed to determine method and timing of testing, precise diagnostic criteria for maternal hypothyroidism, and ways to assure the adequacy and efficacy of therapy.

A randomized controlled antenatal screening study¹⁹ underway in South Wales aims to recruit 22,000 pregnant women.

Is current treatment inadequate?

These observations call into question the adequacy of current therapeutic regimens:

- no significant differences were seen in the IQ scores of children of untreated and treated hypothyroid mothers,¹⁵ and
- infants of treated hypothyroid women demonstrated restricted intrauterine growth and abnormal neonatal thyroid function.²

Take-home message. Although findings indicate hypothyroidism during pregnancy may have an adverse effect on fetal growth and neurodevelopment, evidence is insufficient to

justify universal screening. Still, what we have learned to date enables us to formulate a reasonable monitoring and follow-up protocol (see “Clinical recommendations,” page 33). ■

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