Thyroid Dysfunction in Pregnancy
The Basic Science and Clinical Evidence Surrounding the Controversy in Management

Cynthia Gyamfi, MD, Ronald J. Wapner, MD, and Mary E. D’Alton, MD

Maternal hypothyroidism is known to result in neurodevelopmental disorders in offspring, but whether subclinical hypothyroidism results in lower intelligence quotient (IQ) performance in progeny is an area of debate. Animal studies have shown that fetal thyroxine and triiodothyronine are primarily maternally derived before mid gestation. Other animal data reveal that fetal brain damage at a time that is analogous to the first trimester in humans can be linked to irreversible future brain damage. A large study conducted on an unselected population of pregnant women, both with known diagnosis of hypothyroidism and those who were screened but not diagnosed, found a four-point difference in the IQ levels of the offspring, raising the question of clinical significance. The endocrine community has accepted that subclinical hypothyroidism causes a significant decrease in IQ scores and has advocated for routine screening of pregnant women. However, obstetric authorities have cautioned that more research is needed before a causal relationship between subclinical hypothyroidism and lower IQ performance can be verified. Consequently, the American College of Obstetricians and Gynecologists has stated that routine screening and treatment of subclinical hypothyroidism cannot be recommended. We will review the basic science and clinical evidence for the neurodevelopmental effects of thyroid dysfunction in pregnancy.

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We have known for more than a century that maternal hypothyroidism results in neurodevelopmental disorders in offspring.¹ This observation originated from physicians practicing in areas where iodine deficiency was prominent, suggesting that thyroid hormone was necessary during fetal life. Western-trained physicians practicing in iodine-rich areas did not embrace this theory, partly because of success with the prompt treatment of congenital hypothyroidism.¹ In the past several years, data have emerged to suggest that the presence of thyroid hormone is critical to the brain of the developing fetus.²–⁴ However, in the case of subclinical hypothyroidism, thyroid hormone levels are normal, but thyroid stimulating hormone (TSH) is elevated, leading many to wonder why treating subclinical hypothyroidism would improve fetal outcome. This article will review the data surrounding this controversy.

BACKGROUND

The interest in hypothyroidism and intellectual development in offspring was reawakened after several recent publications addressed a possible relationship between the two.²–⁴ Haddow et al.² performed a case-control study comparing pregnant women with hypothyroidism to pregnant controls with normal thyroid function. They found that children of women with hypothyroidism scored four points lower on a standard intelligence quotient (IQ) test when compared with controls (P<.06). In addition, 15% of cases had an IQ score of 85 or less compared with 5% of controls (P=.08). Although neither of these values is statistically significant, when the results were subanalyzed for those women with untreated hypothyroidism, as opposed to those on medication, they found that the IQ scores were 7 points lower in cases than controls (P=.05), and 19% had IQ scores less than 85 compared with 5% of controls (P=.007), suggesting that the greater effect on pediatric neurodevelopment is in the untreated mothers with hypothyroidism. Pop and colleagues³,⁴ had similar results when they studied pediatric neurodevelopment at 10, 12, and 24
months in children of mothers with abnormal thyroid function at 12 weeks gestation.

There are conflicting position statements regarding surveillance for hypothyroidism in pregnant women from the American Association of Clinical Endocrinologists, the American Thyroid Association, the Endocrine Society, and the American College of Obstetricians and Gynecologists (ACOG).\textsuperscript{5,7} Current obstetric practice does not involve screening for thyroid disease unless the patient has risk factors, such as pregestational diabetes, or is symptomatic. The most recent joint position statement of the three above-mentioned endocrine societies recommends routine thyroid stimulating hormone (TSH) evaluation (with free thyroxine [fT4] if TSH is abnormal) both preconceptionally or as soon as pregnancy has been diagnosed.\textsuperscript{5} However, ACOG does not support the performance of thyroid function tests in asymptomatic pregnant women.\textsuperscript{6–7} The American College of Obstetricians and Gynecologists advises that current data are limited because of their observational nature. To date, there has not been a clinical trial that specifically addresses isolated subclinical hypothyroidism and neurodevelopmental outcomes, making recommendations regarding the management of this mild thyroid dysfunction difficult. Furthermore, the available clinical literature has not shown that the identification and treatment of women with subclinical hypothyroidism prevents the purported neurodevelopmental sequelae.

One of the difficulties in interpreting data on hypothyroidism from different sources is that different definitions of hypothyroidism are used. Harrison’s\textsuperscript{8} textbook of internal medicine defines hypothyroidism as elevated TSH with normal free triiodothyronine (T3) or free T4.\textsuperscript{5} Although this definition is similar to the one used by Harrison’s textbook, subclinical hypothyroidism may not be the most clinically relevant finding. The more clinically relevant thyroid dysfunction may be derived from the animal literature. When evaluating early brain development, investigators identified hypothyroxinemia specifically, and not elevated TSH, as leading to the brain’s alteration.\textsuperscript{9,10} Partly in response to the position of ACOG and because of existing discrepancies in the appropriate management, the Maternal–Fetal Medicine Unit of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development has initiated a prospective, randomized trial to identify and treat women with subclinical hypothyroidism.

**PHYSIOLOGY**

The thyroid develops from the third week of gestation from the primitive pharynx. The gland then migrates to the neck and starts to produce thyroid hormone by 10 to 12 weeks.\textsuperscript{11} The thyroid functions to provide thermal and metabolic regulation.

Maternal thyroid physiology is altered in a normal pregnancy. There is glandular hyperplasia with thyroid enlargement. Thyroid volume is increased on ultrasound examination, but the echo structure is unchanged. The normal increase in the renal glomerular filtration rate causes an increase in urinary iodide clearance, necessitating increased intake of dietary iodine to make and maintain thyroid hormone levels. Because of the similar subunits of chorionic gonadotropin and thyrotropin (TSH), crossover between these two peptides can lead to an increase in fT4 in the first trimester. Elevated fT4 causes suppression of TSH which, in turn, causes barely detectable levels of maternal thyrotropin-releasing hormone (TRH).\textsuperscript{11} These normal physiologic changes make diagnosis of thyroid disease during pregnancy difficult.\textsuperscript{1,9,12}

**Laboratory Studies Evaluating the Role of Thyroid Hormone in Brain Function**

Studies from experimental rat models have helped to elucidate the role of maternal thyroxine (T\textsubscript{4}) in the fetus.\textsuperscript{9,10} Rats are a good comparison group for humans with regard to thyroid function because, like humans, rats have a period early in development where thyroid hormone is provided by the mother.\textsuperscript{1} The thyroid hormone receptor has been identified in rat brains before neural tube closure, which is before active fetal rat thyroid hormone production. Triiodothyronine (T\textsubscript{3}) is made by conversion of maternal T\textsubscript{4}. It has been demonstrated that if maternal T\textsubscript{3} is low, fetal T\textsubscript{3} levels in the brain will be low even in the presence of normal maternal and fetal serum T\textsubscript{4}, suggesting that both T\textsubscript{3} and T\textsubscript{4} in the fetal brain are maternal-T\textsubscript{4} dependent.\textsuperscript{10} Further evidence of a ma-

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**Table 1. Definitions of Thyroid Dysfunction**

<table>
<thead>
<tr>
<th>Function</th>
<th>TSH</th>
<th>Free T4</th>
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<tbody>
<tr>
<td>Clinical hypothyroidism</td>
<td>Elevated</td>
<td>Low</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypothyroxinemia</td>
<td>Normal</td>
<td>Low</td>
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TSH, thyroid stimulating hormone; T\textsubscript{4}, thyroxine.
ternal source of T₃ in the fetal brain is that by mid gestation, fetal concentration of T₃ is 34% of adult levels. This is much higher than would be expected considering the low circulating fetal serum levels.

The expected circulating fetal levels of thyroid hormone were outlined in a study performed by Contempre et al. They punctured human embryonic cavities transvaginally with ultrasound guidance at 6 to 11 weeks, with the goal of obtaining samples that were purely fetal without compromise of the maternal vasculature. They found that fetal T₄ levels were less than 1% of maternal, with fetal T₃ being 10-fold lower than fetal T₄. Variations in fetal T₄ levels, however, still correlated with circulating maternal T₄. These findings were confirmed by this same group of researchers in a subsequent study performed in a similar fashion at 17 weeks of gestation.

Thyroid hormone, specifically free T₄, is present in higher levels in the fetus than expected from fetal production, but what is the function of this hormone once it is there? The presence of thyroid hormone receptors in the fetal brain by 28 days suggests that thyroid hormone mediates some type of biologic effect. Specifically, thyroid hormone concentrates in the cerebral cortex before 20 weeks. Preliminary evidence of the effect of thyroid hormone deficiency on the cerebral cortex was described by Lavado-Bautric and colleagues. The researchers fed rats an iodine-deficient diet, then determined preconceptual T₄ and T₃ levels.1 This is much higher than would be expected from fetal production, but what is the function of this hormone once it is there? The presence of thyroid hormone receptors in the fetal brain by 28 days suggests that thyroid hormone mediates some type of biologic effect. Specifically, thyroid hormone concentrates in the cerebral cortex before 20 weeks. Preliminary evidence of the effect of thyroid hormone deficiency on the cerebral cortex was described by Lavado-Bautric and colleagues. The researchers fed rats an iodine-deficient diet, then determined preconceptual T₄ and T₃ levels. The rats were then mated, and the cell migration and cytoarchitecture of the somatosensory cortex and hippocampus were studied in offspring. They found aberrant neuronal migration in iodine-deficient pups when compared with normal offspring. They also found a “blurring” of the cytoarchitecture, with abnormal morphology.

The same group of researchers then sought to discover whether there was a critical period where the brain was particularly sensitive to maternal thyroid levels or whether the altered neuronal migration was related to the degree of hypothyroxinemia. They treated normal rats with methimazole for 3 days early in their 23-day gestation. This period is analogous to the first trimester in humans, during which time the thyroid gland of human fetuses, like the rat embryos, has not yet started to function. They found that even this transient period of maternal hypothyroxinemia in rats caused irreversible damage during brain development.

Clinical Data Evaluating the Role of Thyroid Hormone in Brain Function

The first report of a possible correlation between thyroid disease and mental retardation in offspring came from iodine-deficient areas of Switzerland in 1915. They noted that mothers of children with mental retardation had abnormal thyroid function and based their report on clinical observations in the region. Choufoer and colleagues then described the effect of maternal thyroid levels on the newborn in 1965. They described pregnancy outcomes related to endemic goiter in iodine-deficient New Guinea. They found neurologic manifestations of cretinism, or physical stunting and mental retardation, in women who were not clinically hypothyroid, but who had a low concentration of thyroid hormone. In this same decade, Man and Jones evaluated a cohort of 1,349 children of mothers with hypothyroxinemia, defined in that time as butanol-extractable iodines with a normal thyroid-binding globulin. They found an association between low butanol-extractable iodines and low infant Bayley scores on mental and motor development. The Bayley scales of infant development were designed to test the cognitive, motor, and behavioral development of infants up to 42 months of age. The test has high validity and reliability. These and other observations of maternal thyroid disease led to the landmark double-blinded study by Pharaoh et al in 1971. They gave alternate families in New Guinea either 4 ml-injections of iodized oil, or a saline placebo, then returned a year later to initiate periodic evaluation of any offspring delivered after treatment. They concluded that supplementation of iodine in pregnancy prevented subsequent cretinism.

Pop and colleagues have studied thyroid disease in pregnancy and the effects on postpartum depression and postpartum thyroiditis. They measured thyroid peroxidase antibodies, free T₄, and other thyroid indices at 32 weeks of gestation in 293 women to evaluate the relationship between thyroid dysfunction and depression. It is from this cohort that they evaluated pediatric neurodevelopment in the children once they reached 5 years of age. They found no difference in pediatric neurodevelopment at 5 years in the group of women with low free T₄ at 32 weeks. They hypothesized that perhaps the greater effect of maternal free T₄ was before fetal production of thyroid hormone at approximately 14 weeks. Therefore, analyzing maternal thyroid levels at 32 weeks may be too late in gestation to evaluate this relationship. Subsequently they initiated a similar study in women from iodine-sufficient areas in the Netherlands at an earlier gestation. They investigated maternal thyroid determinants (fT₃, TSH, and thyroid peroxidase antibody) at 12 and 32 weeks, both before and after fetal contribution to thyroxine levels. Means were evaluated using the Student t test, and both linear and
Table 2. Multivariable Analysis of Factors Related to a Score Less Than 1 Standard Deviation Below the Mean on the Psychomotor Scale of the Bayley Scale of Infant Development

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>TPO-Ab 100 units/mL or more at 12 wk</td>
<td>3.4</td>
</tr>
<tr>
<td>TPO-Ab 100 units/mL or more at 32 wk</td>
<td>1.9</td>
</tr>
<tr>
<td>FT₄ less than 10th percentile at 12 wk</td>
<td>2.5</td>
</tr>
<tr>
<td>FT₄ less than 10th percentile at 32 wk</td>
<td>2.3</td>
</tr>
</tbody>
</table>

CI, confidence interval; TPO-Ab, thyroid peroxidase antibody; FT₄, free T₄.

Results are from the Pop et al⁴ trial (1999).

logistic regression were used for continuous and dichotomous variables. In a multivariable analysis, they found that FT₄ levels below the 10th percentile at 12 weeks of gestation, but not 32 weeks, were independently associated with lower score on the Dutch version of the Bayley Scale of Infant Development when infants were tested at 10 months of age (Table 2).³

In 2003, Pop and colleagues⁴ then tested these same infants to report on the 3-year follow-up. They again performed the Dutch version of the Bayley Scale for Infant Development, testing both mental and motor scores at 1 and 2 years. Comparing means using the Student t test, they found that the infants of mothers with hypothyroxinemia performed significantly worse on both the mental and motor scores (Table 3).

Haddow et al² further elaborated on this theory by evaluating thyroid levels in an unselected group of 25,216 women who had second-trimester prenatal serum screening in Maine. They defined hypothyroidism in two ways. First, they identified all women from this cohort with a TSH above the 99.7th percentile. Then, to increase their population and get a range of milder cases, they included women with a TSH between the 98th and 99.6th percentile who also had a low FT₄. They identified 62 women and compared their 7-to-9-year-old children with 124 matched controls (Table 4). Using the Student t test, they found that children of women with hypothyroidism (by both definitions) scored 4 points lower on the Wechsler Intelligence Scale IQ test when compared with controls (P=.06). In addition, χ² analysis showed that 15% of cases had an IQ score of 85 or less compared with 5% of controls (P=.08). Although neither of these values is statistically significant, when the results were subanalyzed for those women with hypothyroidism who were not receiving treatment, they found the IQ scores were 7 points lower in cases than controls (P=.005), and 19% had IQ scores of less than 85 compared with 5% of controls (P=.007).²

Recently, a study by Vermiglio and coworkers suggested an association between maternal hypothyroxinemia, defined by a normal serum TSH with a low free T₄, and attention deficit hyperactivity disorder (ADHD).²² They studied women from Italy who lived in iodine-deficient areas and compared them with women from iodine-sufficient areas in Italy as controls. They found that ADHD affected 68.7% (11 of 16) of the children in the iodine-deficient areas. None of the control children (0 of 11) was affected. Attention deficit hyperactivity disorder was assessed by parental response to questions on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition-Text Revision, validated for the Italian population. They also assessed maternal thyroid function and found that the overall prevalence of ADHD in mothers with hypothyroxinemia was significantly higher than mothers who were euthyroid, odds ratio 2.34, P=.001.

DISCUSSION

The clinical data certainly suggest that pediatric neurodevelopment is affected by maternal thyroid status, but the current literature does not support routine screening and treatment.⁵,⁶ There are several reasons that clinicians should wait for more data before routine screening and treatment for subclinical hypothyroidism. First, there are limitations to both the Haddow et al² and Pop et al⁴ trials. They studied different populations. Haddow et al intended to study women with hypothyroidism, and they defined this as women with an elevated TSH.² To enhance their population, they then included another group with both elevated TSH and a low free T₄, or overt hypothyroidism by the definition in Harrison’s Textbook of Medicine. Haddow and colleagues did not intend to study subclinical hypothyroidism. Some of the women identified were being treated with thyroid...
replacement medications, and others were not. Although Haddow et al subanalyzed their results to evaluate only those off medication, women with overt hypothyroidism should receive treatment. Although this answers an important question about clinical hypothyroidism and pediatric neurodevelopment, conclusions about subclinical hypothyroidism are nebulous and should not be derived. Pop and colleagues included only those women with a low free \( T_4 \), or hypothyroxinemia, and excluded those with an elevated TSH. Hypothyroxinemia is believed to be the more important population suggested by animal data as it relates to pediatric neurodevelopment. Although Pop et al focused on women with hypothyroxinemia, they only had pediatric follow-up to 2 years of age, and they commented that “infant development at this early age still has only a limited value regarding the prediction of a child’s abilities at a later age,” acknowledging the limitations of their approach.

Next, there are no data to support that treatment of women with subclinical hypothyroidism will improve pediatric neurodevelopment, and the mass screening and treatment of pregnant women should be approached with caution. Not only will this incur substantial cost to the health care system, but medication of asymptomatic women deserves some degree of benefit. We do not know whether levothyroxine works equally well for subclinical disease, nor would we know when to stop the medication if hypothyroxinemia is the outcome we are trying to avoid. Iodine supplementation may be sufficient. The effect of such a mandate is not a small one. According to a review by Casey and colleagues, they estimated an incidence of subclinical hypothyroidism of 2.3% when they screened all pregnant women over a period of 2 and one half years. With a little more than 4,000,000 births in the United States annually, there is a potential for 92,000 affected children from mothers with subclinical hypothyroidism. Testing all of these pregnant women to identify those cases could cost upwards of one hundred million dollars alone, and this does not include the cost of treatment.

Finally, if the link between maternal hypothyroxinemia and pediatric neurodevelopment is established in humans, screening and treatment with levothyroxine may not be the solution. Worldwide, most cases of maternal hypothyroxinemia are related to relative iodine deficiency. Although iodine deficiency has been problematic in the developing world, we now know that maternal intake of iodine has been on the decline in the United States as well. In fact, in the period from 1988 to 1994, 15% of women had urinary iodine excretions below the level at which thyroid secretion becomes overly inadequate. This may be attributed in part to a decrease in the amount of iodine in bread or a decrease in salt intake. Addressing this problem may obviate the issue at hand.

A United States multicenter, randomized trial is currently underway to answer the question of whether screening and treatment of hypothyroxinemia or subclinical hypothyroidism have a long-term effect on pediatric neurodevelopment (clinicaltrials.gov identifier: NCT00388297). We look forward to the results of this trial before considering whether the standard of care in obstetrics should be changed.

### REFERENCES

5. Gharib H, Tuttle RM, Bakin HJ, Fish LH, Singer PA, McDermott MT. Consensus Statement #1. Subclinical thyroid dysfunction: A joint statement on management from the American Associ-


