

COMMENTARY

Hypothyroidism in Pregnancy: Consequences to Neonatal Health

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Maternal and fetal thyroid physiology

Pregnancy influences thyroid function in multiple ways. Not only does the maternal hypothalamic-pituitary-thyroid (HPT) axis undergo a series of adjustments, the fetus develops its own HPT axis and the placenta plays an active role in iodide and T₄ transport and metabolism. Thus, an integrated three-compartment thyroid model exists during gestation (1).

Early in pregnancy estrogen promotes production of a more highly sialylated T₄-binding globulin isoform that is less rapidly degraded, resulting in increased serum T₄-binding globulin and T₄ concentrations (1–3). Although a transient decrease in serum free T₄, followed by a rise in TSH to a new equilibrium, may occur (3), this is usually not appreciated with routine thyroid testing. A high circulating CG level in the first trimester leads to CG cross-reactivity with the TSH receptor, prompting a temporary increase in free T₄ and partial suppression of TSH. The final physiologic change results from placental deiodination of maternal T₄, which increases T₄ turnover. In normal pregnant women, the thyroid gland maintains euthyroidism with only minor fluctuations in serum T₄ and TSH. However, in women with limited thyroid reserve, due to thyroid autoimmunity or iodine deficiency, hypothyroidism can develop (Fig. 1).

Fetal thyroid ontogeny begins at 10–12 weeks gestation and is not complete until delivery; T₄ is not secreted until 18–20 weeks (1, 3). T₄ is critical for many aspects of brain development including neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis, and neurotransmitter regulation (4). Although these requirements evolve over months (5), an especially critical time is the second trimester (6).

Contrary to past belief, thyroid hormone crosses the placenta. Animal studies have shown that maternal T₄ reaches the fetus (5). T₄ has been measured in human coelomic fluid as early as 4 weeks gestation (7) and is detectable in cord blood of newborns with athyreosis or thyroid dysgenesis (8).

Causes of thyroid dysfunction

Abnormal thyroid gland function may be restricted to the fetus, the expectant mother, or both (Table 1). Fetal hypothyroidism can be permanent or transient. When transient, it results from transplacental passage of autoantibodies or drugs, or to immaturity of the HPT axis in premature infants. Combined maternal and fetal hypothyroidism is almost always due to iodine deficiency (2, 3, 6), but thyroid-binding inhibitory immunoglobulin (TBII) has been implicated on occasion (9). Severe maternal hypothyroidism is not common, but mild thyroid failure in which the serum TSH is elevated with a normal free T₄ level has been reported in 2.5% of pregnancies (10).

The impact of severe iodine deficiency or congenital hypothyroidism on the fetus and newborn is profound, as are the effects of overt maternal hypothyroidism on pregnancy. The severity, timing of onset and duration, as well as post-natal management, all influence fetal and neonatal brain development. It is now believed that even mild maternal hypothyroidism (from mild iodine deficiency, thyroid autoimmunity, or thyroid under-replacement) may affect fetal brain development. The implications of this finding are yet to be clearly defined, but have raised many questions that need resolution.

Effects on fetal health and neurodevelopment: background

Fetal hypothyroidism. Congenital hypothyroidism (CH) affects approximately 1 in 4000 newborns. Eighty-five percent are sporadic cases of thyroid dysgenesis. Next in frequency are genetic disorders, with reported mutations of the genes for PAX-8, thyroid transcription factor 2, TPO, thyroglobulin, sodium-iodide symporter, and others (9).

Before the early 1970s, 40% of children with CH required special education. Neonatal screening programs are now implemented throughout the industrialized world and have reduced the need for special education to only 10% of CH children (11). A meta-analysis of seven studies showed a significant decrease of 6.3 IQ points in 675 CH children vs. 570 controls (12). The severity and duration of fetal hypothyroidism reflect the level of intellectual impairment, and can be assessed by serum T₄ and skeletal maturation at birth. Those newborns with T₄ less than 2 µg/dL and knee bone

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TABLE 1. Causes of maternal and fetal hypothyroidism

Fetal
Congenital
TBII (transient)
Antithyroid drugs
Prematurity
Maternal and fetal
Iodine deficiency (severe, mild/moderate)
TBII
Maternal (overt, subclinical)
Autoimmunity
Postthyroidectomy

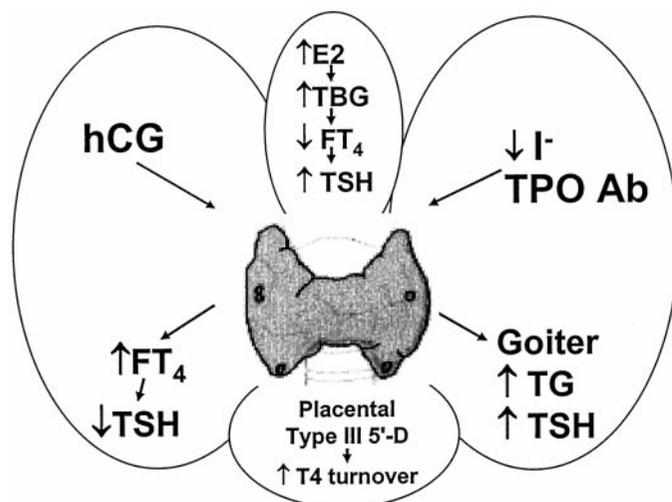


FIG. 1. Physiologic and nutritional influences on maternal thyroid function (see Refs. 2 and 3 for review). The sizes of the circles do not imply relative importance of each biochemical or physiologic pathway.

surface area less than 0.05 cm² have IQs in childhood that are 12–16 points lower than those with milder CH (9).

Derksen-Lubsen and Verkerk (12) suggested that “at least part of the brain damage in patients with CH is caused *in utero* and cannot be prevented by early treatment.” However, two changes in management, earlier treatment, and higher dose L-thyroxine therapy may abrogate or ameliorate any impact of thyroid hormone deficiency on intellectual development (9, 11). Rovet (4) reported the long-term outcome in a group of affected children older than 13 yr of age and found their mean IQ was 8.5 points lower than controls. These adolescents had deficits in memory and in visuospatial and motor abilities, the presence of which correlated with the severity of the CH. Furthermore, 30% of these adolescent patients were not receiving an adequate L-thyroxine dose.

Fetal hypothyroidism can be transient. Transplacental passage of thyrotropin receptor blocking antibody occurs in some women with thyroid autoimmunity (9). Whether there are lasting effects on the offspring, whose hypothyroidism typically resolves within a few months of birth, is unclear. Antithyroid drugs also cross the placenta and may result in fetal goiter and TSH elevations on cord blood. In one study, IQ tests at ages 4–25 yr were the same in children of mothers who received methimazole or propylthiouracil during pregnancy as euthyroid controls (13).

Premature infants also have low T₄ and T₃ levels in the first

few weeks of life. Many factors contribute, including immaturity of the HPT axis, nutrition, and nonthyroidal illnesses (14, 15). There is debate as to whether this hypothyroxinemia is physiologic, or should be treated. Reuss *et al.* (16) reported an increased risk of cerebral palsy and decreased IQ in infants with severe hypothyroxinemia. Van Wassenaer *et al.* (17), showed an improvement up to age 2 in mental and psychomotor development with 6 weeks of L-thyroxine therapy, but only for newborns less than 27 weeks gestation.

Maternal and fetal hypothyroidism

Combined maternal and fetal hypothyroidism occurs mostly in regions with dietary iodine deficiency. The most severely affected infants have neurologic cretinism, manifested by mental retardation (mean IQ, ~29) and impaired gait and motor function (6). Whereas children from these areas may have normal school performance, impaired motor and visual perceptive abilities have been reported (18). These abnormalities have been associated with maternal T₄, but not T₃, levels during pregnancy (19). Furthermore, iodine treatment as early as the first or second (but not third) trimester improves neurologic outcome of the child (20).

In recent years the potential impact of mild to moderate iodine deficiency on the fetus has been recognized. Effects on the mother and fetus include thyroid enlargement and an increase in serum thyroglobulin. Although the mother also has a relative hypothyroxinemia, the fetus maintains a normal free T₄ and TSH (2). School achievement may be impaired, and a variety of neuropsychointellectual deficits have been described (3). Iodine supplements (100–200 µg/day) during pregnancy relieve the stress of iodine deficiency on both maternal and fetal thyroid function, with a decrease in serum thyroglobulin and thyroid gland volume (2). Whether there is an improvement in neurocognitive measures requires further study.

Countries traditionally believed to have sufficient iodine, such as the United States, cannot remain sanguine. A recent National Health and Nutrition Examination Survey showed a considerable increase in the percentage of women with low urinary iodine excretion over a period of 20 yr (Fig. 2; Ref. 21). Although this change is well below the WHO definition of moderate iodine deficiency (20% of the population), the findings demonstrate that a small percentage of expectant mothers are at risk of thyroidal effects as discussed above.

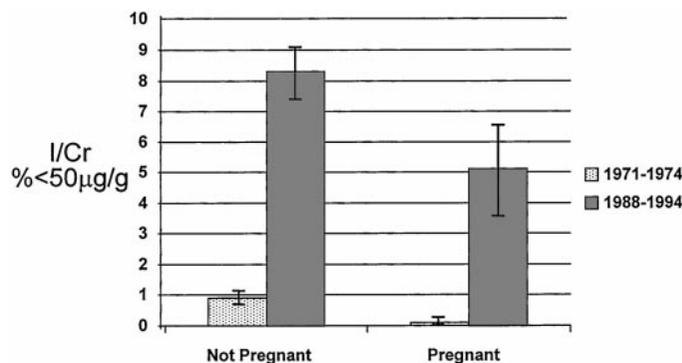


FIG. 2. Iodine nutrition in United States women of childbearing age. Median (\pm SE) concentrations of urinary iodine (percentage with iodine excretion $< 50 \mu\text{g/g}$ creatinine). Data are obtained from Ref. 21.

Maternal hypothyroidism

The frequency of mild and overt hypothyroidism among pregnant women was described by Klein *et al.* (10), who found a serum TSH level greater than 6 mIU/L in 2.5% (49 of 2,000) of women at 15–18 weeks gestation. Overt hypothyroidism (*i.e.* an elevated serum TSH plus a T_4 2.5 SD below the mean or lower) was present in 0.3% of women. Glinoe (2) found an elevated serum TSH concentration in 2.2% of 1,900 pregnant women. Sixteen of those 41 (19%) women had anti-TPO antibodies. In contrast, Fukushi *et al.* (22) detected a high serum TSH concentration in only 0.14% (102 of 70, 632) of Japanese women.

In North America, maternal hypothyroidism is mainly due to autoimmune thyroid disease. Untreated hypothyroidism is associated with several complications, most notably pre-eclampsia and low birth weight, but also abruptio placentae and increased risk of spontaneous miscarriage and perinatal mortality. Treatment with L-thyroxine reduces the complications substantially (23).

Although effects of maternal hypothyroidism on fetal brain development are not well defined, several recent reports indicate that IQ is modestly affected (24–26). These studies have increased the concern that even mild hypothyroidism can interfere with normal brain development. Indeed, several authors have proposed screening programs for thyroid dysfunction during or even before pregnancy. The economic impact is not inconsequential, and so it is important to understand not only the underlying potential problems but also the goals of intervention.

Man *et al.* (24), in the 1970s, studied the effects of hypothyroidism and thyroid hormone replacement on IQ. Using the butanol extractable iodine (BEI) test as a measure of serum T_4 , they found that 3% of 1349 pregnant Rhode Island women were “hypothyroxinemic” (low BEI). Mean IQ of their offspring at 4 and 7 yr was lower by 6 and 5 points, respectively, than children of euthyroid women. At age 7, the IQs of children whose mothers had a low BEI were less than 80 in 24% *vs.* only 10% of control children. Furthermore, thyroid hormone therapy apparently prevented these effects on IQ. The iodine status and prevalence of thyroid autoimmunity in these mothers were not studied.

In 1999, Pop *et al.* (25) tested mental and psychomotor development in 220 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 increased risk of delayed psychomotor development (relative risk, 5.8). These mothers were three times as likely to be TPO antibody positive (25% *vs.* 8%). However, there were other potential factors beyond hypothyroxinemia that may have contributed to the neurocognitive abnormalities described. Major depression, a known risk factor for impaired childhood development, was present in some mothers. In a previous study, those authors reported that impaired development based on the Gestalt Cognitive Scale at 5 yr of age was observed in children whose mothers were anti-TPO antibody positive but with entirely normal thyroid function (27).

The same year, Haddow *et al.* (26) did neuropsychological testing in 62 offspring (of 25,216 women screened) whose

mothers were retrospectively found to have a serum TSH greater than the 99.7th percentile ($n = 47$) or a TSH at the 98–99.6th percentiles with T_4 less than 7.75 $\mu\text{g}/\text{dL}$ ($n = 15$). Mean total and free T_4 levels were also 30% lower in the hypothyroid mothers. Forty-eight of the 62 women received no L-thyroxine during pregnancy. The IQs of children born to affected mothers were 7 points lower than those of controls. Furthermore, the full scale IQ was less than 85 in 19% of affected offspring *vs.* 5% born to euthyroid mothers. Fourteen mothers had been treated with an inadequate dose of thyroid hormone during pregnancy with resulting serum TSH and free T_4 levels that were similar to the 48 untreated women. Nevertheless, the mean IQ of children born to treated mothers was normal, and no child had an IQ less than 85. TPO antibody was present in 77% of the 62 hypothyroid women and in 14% of 125 control women.

A recent report by Smit *et al.* (28) described the status of infants whose mothers had subclinical hypothyroidism. They found a decrease in the mental development index at 6 and 12 months, but not 24 months. Psychomotor development and neurophysiologic and neurologic assessments were unaffected. There is one study showing no effect of severe first trimester hypothyroidism (low T_4 : TSH, 25–190 mU/L) when mothers had normal thyroid function later in pregnancy and children had IQ tests at age 4–10 yr (29).

The importance of monitoring pregnant women with known thyroid dysfunction, including those being treated with L-thyroxine, has been recognized for more than 10 yr. A recent review of 17 articles found that 10.0% (range, 2.8–19.6) of 12,592 women were positive for microsomal or TPO antibody during or shortly after pregnancy (30). Many of these women may have decreased thyroid reserve that would lead to maternal and fetal hypothyroidism in the setting of an increase in T_4 catabolism during pregnancy. Furthermore, many women with known hypothyroidism that is being treated will have a substantially increased T_4 dose requirement (31). In our review of four series (total of 108 women), serum TSH increased in 58%. The mean L-thyroxine dose increased from 117 μg to 150 μg (Table 2).

Future directions

Fetal hypothyroidism. Neonatal screening for CH has had a remarkable impact worldwide on the intellectual development of affected children. Long-term studies of the first generation of treated patients, however, has documented persistent neuropsychological deficits (4), and IQs remain below average in those with the most severe hypothyroidism (9, 12).

Recent changes in management (earlier therapy and higher L-thyroxine dose) may eliminate the residual deficits seen in some children and adolescents. Additional studies

TABLE 2. Hypothyroidism in pregnancy, L-thyroxine therapy

First author	No.	↑ TSH	L-thyroxine dose (μg)	
			Before	During
Mandel (33)	12	9	102	148
Girling (34)	34	7	124	138
Kaplan (35)	42	27	112	154
McDougall (36)	20	20	125	161
Total	108	63 (↑ 58%)	117	150 (↑ 28%)

are needed to clarify the degree of improvement in affected children's intellectual development, as well as their educational and vocational achievements as adults (4). Higher-dose L-thyroxine therapy has been associated with attention span problems and altered skeletal growth, possibly a consequence of overtreatment (9). Assiduous monitoring of serum T₄ and TSH, especially during the first few years, but also throughout childhood and adolescence, is clearly essential.

Whether transient hypothyroxinemia of prematurity is a condition requiring intervention is under investigation. Several studies have demonstrated impaired neurological outcomes (16). One has shown improved short-term outcomes for very premature infants treated with L-thyroxine for 6 weeks (17). Further research is needed to confirm the original findings, determine the threshold free T₄ level for diagnosis, and establish the optimal L-thyroxine dose required (14). The possible value of T₃ may warrant study, and follow-up of these infants into later childhood will be important.

Maternal and fetal hypothyroidism

Severe iodine deficiency is a major international health problem. Benefits of injections of iodized oil in villages with endemic cretinism are substantial, with a great reduction in numbers of cretins (6). Additional factors impairing thyroid function, such as selenium deficiency and thiocyanate ingestion, complicate the success of iodine prophylaxis in some settings. Therapy before or in early pregnancy is the goal, because increasing maternal T₄ before the second trimester provides the fetus with T₄ early in brain development (6, 20).

Identification of mild neurologic/performance deficits in countries with mild to moderate iodine deficiency has prompted health professionals to encourage adequate iodine intake during pregnancy. The WHO recommends 200 µg/day for pregnant women (3). Whereas several studies have shown reduction in thyroid stress with iodine, effects on maternal T₄ are less well established (2). In one study, 100 µg potassium iodide largely prevented the rise in maternal TSH, but did not increase free T₄. This raises several questions. What is the minimum necessary dose of iodine required? Should women be monitored with urinary iodine to assure compliance, and, if so, what is the threshold for adequate intake? Do some women need L-thyroxine in addition to iodine?

The recognition that 1 in 20 pregnant women in the United States has low urinary iodine raises additional questions. What factors account for this subset of women (*e.g.* socioeconomic status, dietary habits, race)? Should testing be used to identify these women, or should iodine supplements be given to all pregnant women in the United States? The *Physicians' Desk Reference* (2001 edition) lists 17 prescription prenatal vitamins; only 6 (35%) contain potassium iodide. A survey in two pharmacies of over-the-counter preparations, which many women choose to purchase, identified 24 multivitamin preparations, only 16 (67%) of which contained iodine (data not shown). Physicians, therefore, need to be aware of what their patients are taking if they are felt to be iodine deficient.

It is also important to recognize that while mild neurologic

abnormalities have been identified, it remains to be proven that iodine supplements alone will prevent these changes.

Maternal hypothyroidism

Thyroid autoimmunity is common in young women. As noted above, studies have shown a 3–20% prevalence of circulating thyroid antibodies in women during or shortly after pregnancy (30). These women are at risk of becoming hypothyroid during pregnancy (2, 3).

Concern about impaired intelligence and psychomotor development (24–26) has led to the suggestion that women should be screened for hypothyroidism, either by serum TSH (3, 26) or free T₄ (5, 25). This raises several important questions. First, which thyroid function testing strategy should be used? And when? TSH is the usual first-line test. However, some patients may be missed because CG suppresses TSH in early pregnancy. Free T₄ may be the preferred test because it is maternal relative hypothyroxinemia, not a mild TSH elevation, that puts the fetus at risk (5, 25). There is merit to the latter recommendation, since women in the report by Haddow *et al.* (26) also had a 30% reduction in serum T₄. In fact, those with the mildest TSH increases were selected specifically because they also had a low total T₄. Furthermore, before instituting a free T₄ screening program, it would be necessary to determine the normal range for free T₄ in all three trimesters for each diagnostic product used. An increased risk of fetal deaths in women with TSH equal to or greater than 10 mIU/L has been reported (32). The small number of fetuses (*n* = 3) and high prevalence of autoimmunity (80%) that is associated with increased miscarriages (2) leaves unclear the causality of this observation.

Second, is maternal hypothyroxinemia alone responsible for the effects on the intellect of their progeny, or could autoimmunity itself contribute? Pop *et al.* (27) reported a 10-point IQ reduction in preschool children whose mothers were antimicrosomal antibody positive, but who had normal thyroid function while pregnant. Thyroid autoantibody positivity was increased 3-fold in the women with lowest free T₄ values (25) and 5-fold in women whose TSH was increased (26). Another variable is the impact of maternal hypothyroidism that develops after delivery. Haddow *et al.* (26) noted that the median time to diagnosis of hypothyroidism after delivery was 5 yr. What effect might this unrecognized maternal illness have on childrearing during the first 5 yr of life?

Third, are the abnormalities described in the children of hypothyroid mothers permanent? In the report by Haddow *et al.* (26), children were tested at ages 7–9 yr. Whether the prolonged period of maternal hypothyroidism contributed to these persistent deficits is unknown. Pop *et al.* (25) studied infants at 10 months; longer follow-up will be of great interest. Smit *et al.* (28) found mild abnormalities up to a year, which reverted toward normal by age 2.

Fourth, there is no randomized trial showing that L-thyroxine therapy during pregnancy will prevent the changes described above. It would be difficult to justify such a study in women whose TSH is elevated, because that marker is generally assumed to indicate mild thyroid failure. However, it is not clear whether women with the lowest free T₄ levels (many of whom have a serum TSH level in the

normal range) are jeopardizing the optimum intelligence of their offspring. A well-designed clinical trial is needed to provide information that could profoundly influence the management of pregnant women.

Finally, in the absence of clear-cut answers, what should physicians be recommending to their patients now? Certainly women should be counseled on the importance of adequate iodine intake. Unless one knows a patient's dietary ingestion or measures urinary iodine, then assuring compliance with an iodine-containing prenatal vitamin should be the goal. Identifying women at risk of autoimmune thyroid disease, based on the presence of goiter or a personal or family history of thyroid disease or other autoimmune diseases, and carefully monitoring women on thyroid hormone to guarantee normal TSH levels throughout pregnancy, are also extremely important.

Decision and cost-effectiveness studies will help define the impact of universal screening (either with TSH, free T₄, TPO, or some combination) on the health care system. Such an analysis would be strengthened by future studies that more clearly identify the causal relationships between mild thyroid hormone deficiency and thyroid autoimmunity, on the one hand, and fetal neurological development on the other.

In the meantime, physicians and obstetricians must do what they have to so often when evidence is incomplete: use their own judgment about the optimal management for their individual patients.

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