Perinatal Significance of Isolated Maternal Hypothyroxinemia Identified in the First Half of Pregnancy

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OBJECTIVE: To establish pregnancy-specific free thyroxine thresholds and to assess perinatal effects associated with isolated maternal hypothyroxinemia identified in the first half of pregnancy.

METHODS: Stored serum samples from 17,298 women who previously underwent thyroid-stimulating hormone (TSH) screening in the first half of pregnancy were analyzed for free thyroxine (T_4) concentrations and thyroid peroxidase antibodies. Women with a free T_4 below 0.86 ng/dL but a normal-range TSH were identified to have isolated maternal hypothyroxinemia. Pregnancy outcomes in these women were compared to those with a normal TSH and free T_4. Thyroid peroxidase antibody status and the relationship between TSH and free T_4 were analyzed for these women and women with subclinical hypothyroidism.

RESULTS: Isolated maternal hypothyroxinemia was identified in 233 women (1.3%). There were not any excessive adverse pregnancy outcomes in these women. Positive thyroid peroxidase antibody assays (greater than 50 international units/mL) were similar in normal women (4%) and those with isolated hypothyroxinemia (5%) but were greater in women with subclinical hypothyroidism (31%, $P<.001$). There was a negative correlation between TSH and free T_4 in normal women ($r_s=-0.19$, $P<.001$) and those with subclinical hypothyroidism ($r_s=-0.11$, $P=.007$). The correlation in women with isolated hypothyroxinemia was not significant.

CONCLUSION: Isolated maternal hypothyroxinemia has no adverse effects on perinatal outcome. Moreover, unlike subclinical hypothyroidism, there was a low prevalence of thyroid peroxidase antibodies and no correlation between TSH and free T_4 levels in women with hypothyroxinemia, leading us to question its biological significance.

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LEVEL OF EVIDENCE: II

Publication of two studies during 1999 provoked a number of concerns about conventional thinking regarding maternal–fetal thyroid pathophysiology. In one study from the United States, Haddow and colleagues[1] described a cohort of children born to women identified to have either mild clinical hypothyroidism or subclinical hypothyroidism. Although these investigators did not differentiate between the two maternal conditions, their aggregate analyses led them to conclude that children born to these mothers were at risk for impaired neurodevelopment. In the other study from the Netherlands, Pop and associates[2] identified a cohort of women who at 12 weeks of gestation had a low serum free thyroxine level along with a normal thyrotropin concentration. Offspring of women with what we refer to as *isolated maternal hypothyroxinemia* were found to have lower psychomotor scores at 10 months of age as well as impaired neurodevelopment at 2 years when compared with normal controls.[3] Subsequently, we reported pregnancy outcomes in 17,000 women who underwent thyrotropin screening during the first half of pregnancy. Women with subclinical hypothyroidism were found to have significantly increased rates of preterm delivery and placental abruption along with their associated neonatal morbidity.[4]

Before these reports, screening for maternal thyroid disorders during pregnancy was based on histor-

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ical risk factors and clinical findings.[5] Prompted by the observations of Haddow et al and after considerable debate, a number of national endocrine societies revised their guidelines to recommend universal prenatal screening with thyrotropin levels to identify women with subclinical hypothyroidism.[1,6–8] Some of these societies, albeit without evidence of improved outcomes, also recommended thyroxine replacement for subclinically hypothyroid women.[9] At the same time, isolated maternal hypothyroxinemia[2,3] has not stimulated similar recommendations for prenatal screening with serum free thyroxine levels. Despite this, establishment of pregnancy-specific free thyroxine thresholds has been considered a high-priority research objective to assist continuing efforts to determine the clinical validity of screening for thyroid deficiency.[9]

The present study was designed to establish pregnancy-specific free thyroxine thresholds and to assess perinatal effects associated with isolated maternal hypothyroxinemia identified in the first half of pregnancy. To accomplish this we retrieved stored serum samples taken from more than 17,000 women who had previously undergone thyrotropin screening.[4,10] After constructing a gestational age–specific nomogram for serum free thyroxine concentrations, we compared pregnancy outcomes of women with isolated hypothyroxinemia with those of women with normal thyroid test values. To assess similarities between isolated hypothyroxinemia and subclinical hypothyroidism, we assayed these samples for thyroid peroxidase (TPO) antibodies to evaluate their prevalence in both conditions as well as in normal pregnant women. Finally, we analyzed the correlation between serum thyroid-stimulating hormone (TSH) and free thyroxine (T_4) concentrations in pregnant women with isolated hypothyroxinemia and subclinical hypothyroidism and compared both with women with normal thyroid tests.

MATERIALS AND METHODS

With the approval of the institutional review boards at the University of Texas Southwestern and Parkland Hospital, excess serum from blood tested for rubella antibody was delivered to a research laboratory for TSH level determination. Serum from women tested from November 1, 2000 to April 14, 2003 that had TSH values outside the normal range were reflexively assayed for free T_4.[4] Women with both a high TSH and a low free T_4 serum level were referred for further evaluation and treatment. Chemiluminescent immunoassays were used to determine TSH and free T_4 concentrations (Immulite 2000 Analyzer, Diagnostic Products Corporation, Los Angeles, CA). The analytical sensitivity of the TSH assay was 0.002 milliunits/L, and its coefficient of variation was 3.8% within run and 4.6% between runs using specimens in the normal range. Stability of the analyte was assessed through 10 cycles of freezing and thawing in five specimens, yielding a coefficient of variation of 6.5% for TSH. The sensitivity limit for free T_4 was 0.18 ng/mL, with a within-run coefficient of variation of 7.1% and between-run coefficient of 6.4%. Excess serum was frozen and stored at −80°C.

For the present study, serum samples were retrieved in women who had been screened in the first 20 weeks of gestation and who were delivered of a singleton infant weighing 500 g or more. Serum aliquots were analyzed for concentrations of free T_4 and thyroid peroxidase antibodies. Previously published gestational age–specific thresholds for the 2.5th and 97.5th percentiles were used to establish a single lower TSH threshold of 0.08 milliunits/L and an upper TSH threshold 3.0 milliunits/L and are shown in Figure 1A.[4,10] This upper threshold was chosen to minimize the number of women with subclinical hypothyroidism that would be missed, because the 97.5th percentile values for the TSH during first half of pregnancy ranged from 5.09 to 2.74 milliunits/L. Upper (1.9 ng/dL) and lower (0.86 ng/dL) free T_4 thresholds were similarly determined and are shown in Figure 1B. Women with serum free T_4 values below 0.86 ng/dL, but a normal range TSH level (0.08–2.99 mU/L), were identified to have *isolated maternal hypothyroxinemia.* Women with a TSH level of 3.0 milliunits/L or greater and a normal range free T_4 were identified to have *subclinical hypothyroidism.*

Pregnancy outcomes in women identified with isolated maternal hypothyroxinemia and in women with subclinical hypothyroidism were compared with those who had normal levels of both TSH and free T_4. Selected obstetric and neonatal outcomes for all women delivering infants at Parkland Hospital are routinely entered into a computerized perinatal database. Nurses attending each delivery complete an obstetric data sheet, and research nurses assess the data for consistency and completeness before electronic storage. Data on infant outcomes are abstracted from discharge records and entered into a separate database. Thyroid function study results were electronically linked to the perinatal and infant outcomes databases. Gestational age was established using a previously described method that has been found to correlate well with ultrasonographic and pediatric estimates in our obstetric population.[10,11] Gestational hypertension was defined as an intrapartum blood

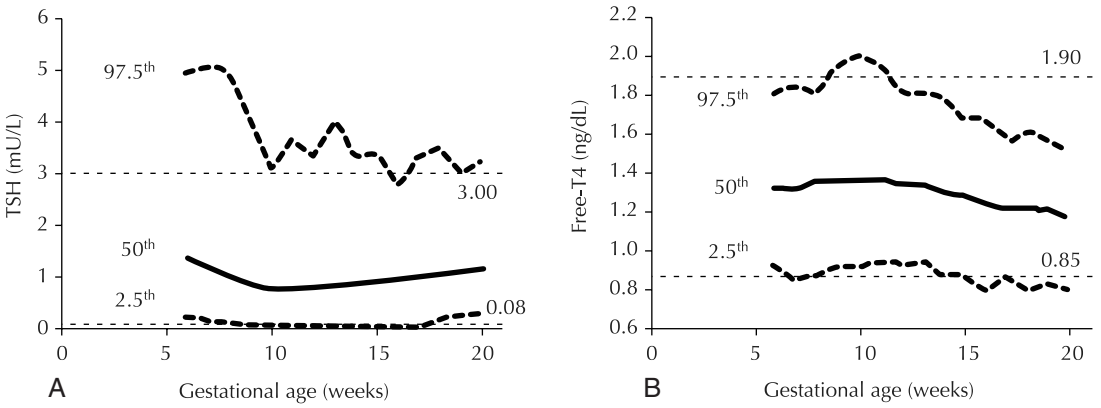

Fig. 1. Gestational age-specific nomograms for serum thyroid-stimulating hormone **(A)** and free thyroxine **(B)** levels derived from serum samples from 17, 298 women tested at 20 weeks of gestation or less. The solid lines represent the 50th percentile and the dashed lines represent the 2.5th and 97.5th percentiles according to gestational age in weeks. The dotted lines represent the reference ranges for thyroid-stimulating hormone **(A)** and free thyroxine **(B)**. TSH, thyroid-stimulating hormone; T_4, thyroxine.

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pressure of 140/90 mm Hg or greater. Severe preeclampsia was diagnosed in hypertensive women who had at least one of the following: blood pressure more than 160/110 mm Hg, serum creatinine more than 1.0 mg/dL, platelet count less than 100,000/μL, serum aspartate aminotransferase level at least twice the upper normal value, persistent headache or scotomata, 2+ or more dipstick proteinuria, or more than 2 g of protein excreted in 24 hours. Infants with major malformations included those with aneuploidy, an identifiable syndrome, and those with an anomaly involving a principal organ system.[12]

Serum thyroid peroxidase antibody levels were determined using a chemiluminescent assay (Immulite 2000 Analyzer, Diagnostic Products Corporation). The analytical sensitivity was 5.0 international units/mL, and its coefficient of variation was 9.8% within run and 11.3% between runs. Normal values for TPO antibody levels were 50 international units/mL or more. Finally, the relationship between serum TSH and free T_4 levels was analyzed for women with isolated hypothyroxinemia, subclinical hypothyroidism, as well as for those with both TSH and free T_4 within the normal reference ranges.

Pearson's χ^2 and Student t test were used for univariable two-group comparisons. Spearman correlations were used to evaluate the association between continuous measures. Logistic regression was applied to examine the significance for selected pregnancy outcomes adjusted for maternal age, race, parity, and weight. The Hosmer-Lemeshow statistic was used to examine the goodness-of-fit for the logistic regression model. Statistical computations were performed using SAS 9 (SAS Institute, Cary, NC). Two-tailed P values less than .05 were judged statistically significant.

RESULTS

Between November 1, 2000 and April 14, 2003, 25,765 women with a singleton pregnancy who presented to Parkland Hospital for prenatal care underwent thyroid screening. The current study includes 17,298 women who presented for prenatal care during the first 20 weeks of gestation. The mean gestational age at screening was 11.9±3 weeks and ranged from 6 to 20 weeks of gestation. Of these, 233 women (1.3%) were identified to have isolated maternal hypothyroxinemia. Another 598 (3.4%) were diagnosed with subclinical hypothyroidism. Shown in Figure 1A are the 97.5th and 2.5th percentile thyrotropin values corrected for gestational age and used to establish single upper (3.0 milliunits/L) and lower (0.08 milliunits/L) thresholds for the first 20 weeks of pregnancy.[10] The 97.5th and 2.5th percentile values for free T_4 corrected for gestational age and used to establish single upper (1.9 ng/dL) and lower (0.86 ng/dL) thresholds for the first half of pregnancy ranged between 1.52 and 1.91 ng/dL, and, 0.77 and 0.92 ng/dL, respectively (Fig. 1B).

Maternal characteristics of women with isolated hypothyroxinemia or subclinical hypothyroidism are compared with women whose TSH and free T_4 levels were within the normal reference ranges. As shown in Table 1, women with isolated maternal hypothyroxinemia were older, heavier, and more often multipa-

Table 1. Maternal Characteristics of Pregnant Women Who Presented for Prenatal Care at or Before 20 Weeks of Gestation and Identified to Have Either Isolated Hypothyroxinemia or Subclinical Hypothyroidism Compared With Women With a Normal Thyroid-Stimulating Hormone Level and Free Thyroxine

Maternal Characteristics	Isolated Hypothyroxinemia (n=233)	*P*	Normal TSH, Free T_4 (n=16,011)	*P*	Subclinical Hypothyroidism (n=598)
Age (y)	27.5±6	<.001	25.5±6	<.001	26.6±6
35 or older	32 (14)	<.001	1,178 (7)	.046	57 (9.5)
Race or ethnicity		.06		<.001	
Hispanic	188 (81)		13,727 (86)		515 (86)
African American	32 (14)		1,643 (10)		40 (7)
White	9 (4)		318 (2)		17 (3)
Other	4 (2)		323 (2)		26 (4)
Multiparous	165 (70)	.03	10,235 (64)	0.49	374 (63)
Weight (lbs)	178±42	.006	171 ± 33	<.001	176±39
BMI (kg/m^2)	33±6	.02	32 ± 6	.0014	32±5

Data are mean±standard deviation or n (%).
TSH, thyroid-stimulating hormone; T_4, thyroxine; BMI, body mass index.

rous than women in the normal cohort. Women with subclinical hypothyroidism were also older and heavier than control women, and were less likely to be black and more likely of "other" ethnicity. Shown in Table 2 are pregnancy outcomes in women with subclinical hypothyroidism or isolated hypothyroxinemia compared with women with normal thyroid values. Women with isolated hypothyroxinemia and those with normal TSH and free T_4 values had similar rates of adverse pregnancy outcomes. This was also true when gestational age–specific 2.5th percentile thresholds were used to identify women with isolated hypothyroxinemia (data not shown). Women with subclinical hypothyroidism, however, had a higher incidence both of placental abruption and preterm birth when compared with the normal cohort. They also had a higher incidence of diabetes, and 43 (78%) of these 55 women were diagnosed with gestational diabetes. This difference persisted after adjustment for maternal age, race, parity, and weight (odds ratio 1.47, 95% confidence interval 1.1–2.0).

Neonatal outcomes are shown in Table 3. With one exception, there was no increase in neonatal complications associated with isolated maternal hypothyroxinemia. The exception was that infants of women with isolated maternal hypothyroxinemia were more likely to have a grade 3 or 4 intraventricular hemorrhage (0.4 compared with 0.1%. *P*=.04).

Table 2. Pregnancy Outcomes of Pregnant Women Who Presented for Prenatal Care at or Before 20 Weeks of Gestation and Identified to Have Either Isolated Hypothyroxinemia or Subclinical Hypothyroidism Compared With Women With a Normal Thyroid-Stimulating Hormone Level and Free Thyroxine

Pregnancy Outcomes	Isolated Hypothyroxinemia (n=233)	*P*	Normal TSH, Free T_4 (n=16,011)	*P*	Subclinical Hypothyroidism (n=598)
Hypertensive disorders					
Gestational hypertension	18 (8)	.53	1,422 (9)	.68	56 (9)
Severe preeclampsia	10 (4)	.48	851 (5)	.45	36 (6)
Diabetes	10 (4)	.49	850 (5)	<.01	55 (9)
Placental abruption	1 (0.4)	.75	50 (0.3)	.03	5 (1)
Weeks of gestation at delivery					
36 or less	14 (6)	84	913 (6)	.09	44 (7)
34 or less	4 (2)	.44	403 (2.5)	.005	26 (4.3)
32 or less	2 (1)	.47	227 (1)	.13	13 (2.2)
Cesarean delivery	59 (25)	.79	3,934 (25)	.57	153 (26)

TSH, thyroid-stimulating hormone; T_4, thyroxine.
Data are n (%).

Table 3. Neonatal Outcomes in Women Who Presented for Prenatal Care at or Before 20 Weeks of Gestation and Identified to Have Either Isolated Hypothyroxinemia or Subclinical Hypothyroidism Compared With Women With a Normal Thyroid-Stimulating Hormone Level and Free Thyroxine

Neonatal Outcome	Isolated Hypothyroxinemia (n=233)	*P*	Normal TSH, Free T_4 (n=16,011)	*P*	Subclinical Hypothyroidism (n=598)
Birth weight (g)					
1,000 or less	1 (0.4)	.73	96 (0.6)	.83	4 (0.7)
2,500 or less	7 (3)	.08	916 (6)	.24	41 (7)
4,000 or more	30 (13)	.32	1,740 (11)	.09	52 (9)
Intensive care nursery	3 (1.3)	.32	360 (2.2)	.005	24 (4)
5-Min Apgar score 3 or less	0	.2	111 (0.7)	.02	9 (1.5)
Umbilical artery blood pH less than 7.0	7 (3)	.1	263 (1.7)	.91	10 (1.8)
Respiratory distress syndrome*	3 (1.3)	.78	243 (1.5)	.05	15 (2.5)
Necrotizing enterocolitis†	0	.79	5 (0.1)	.09	1 (0.2)
Intraventricular hemorrhage‡	1 (0.4)	.04	11 (0.1)	.38	1 (0.2)
Major malformations	1 (0.4)	.31	181 (1.1)	.77	6 (1.0)
Fetal death	0	.28	79 (0.5)	.09	6 (1)
Neonatal death	0	.45	39 (0.2)	.21	3 (0.5)

Data are n (%).
TSH, thyroid-stimulating hormone; T_4, thyroxine.
* Ventilator therapy greater than 24 hours of life.
† Necrotizing enterocolitis requiring surgery.
‡ Grade 3 or 4.

This difference, however, did not persist after adjustment for maternal age, parity, race, and weight (relative risk 6.3, 95% confidence interval .81–48.7). When outcomes of infants born to mothers with subclinical hypothyroidism were compared, they were more likely to have a 5-minute Apgar score of 3 or less, they were more frequently admitted to the neonatal intensive care unit, and they more often developed respiratory distress syndrome. Importantly, these differences persisted after adjustment for differences in maternal characteristics.

To ascertain the relationship of thyroid peroxidase antibodies with isolated hypothyroxinemia or subclinical hypothyroidism, we compared these characteristics in the three groups of women. A positive assay for TPO antibodies (more than 50 international units/mL) was found in 11 (5%) women with isolated maternal hypothyroxinemia, 188 (31%) with subclinical hypothyroidism, and 694 women (4%) with normal thyroid studies. The difference between women with subclinical hypothyroidism and those with normal TSH and free T_4 was significant (31% compared with 4%, respectively, $P<.001$).

The relationship between TSH and free T_4 in women identified with either subclinical hypothyroidism or isolated hypothyroxinemia is shown in Figure 2. The correlation between TSH and free T_4 in women with isolated maternal hypothyroxinemia was not significant (Fig. 2A, $r_s=0.06$). Conversely, there was a significant negative correlation between these two analytes in women with subclinical hypothyroidism (Fig. 2B, $r_s=-0.11$, $P=.007$). This negative correlation was also significant in women with a normal TSH and free T_4 level ($r_s=-0.19$, $P<.001$, data not shown).

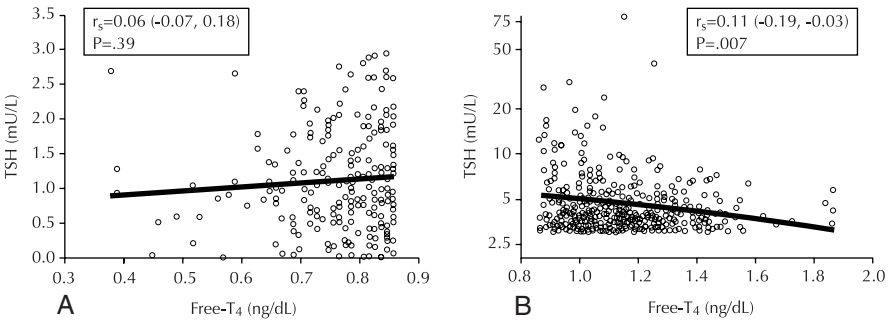

Fig. 2. Correlation between thyroid-stimulating hormone and free thyroxine in 233 women identified with isolated hypothyroxinemia **(A)** and 598 women identified with subclinical hypothyroidism **(B)**. TSH, thyroid-stimulating hormone; T_4, thyroxine.
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DISCUSSION

Using a state-of-the-art assay, we determined upper and lower serum free thyroxine (free T_4) threshold values for 17,298 women in the first half of pregnancy (Fig. 1B). Construction of such a nomogram is a declared goal of a number of national endocrine organizations.[9] As previously reported, free T_4 levels during pregnancy remain within reference ranges reported for nonpregnant adults.[13] These values were used to define isolated maternal hypothyroxinemia as a serum free T_4 level at or less than a threshold representative of the 2.5th percentile across the first half of pregnancy (0.86 ng/dL) accompanied by a serum TSH level in the reference range (0.08–2.99 milliunits/L). As such, the prevalence of isolated maternal hypothyroxinemia was 1.3% in the first half of pregnancy.

Before analyzing this cohort for pregnancy outcomes, we determined the validity of the more pragmatic single upper TSH threshold to include the first half of pregnancy. To do this, we identified women with subclinical hypothyroidism as those with TSH levels of 3.0 milliunits/L or greater accompanied by normal-range free T_4 concentrations (Fig. 1A). The incidence of 3.4% in these 17,298 women was higher than the 2.3% from our previous study for which we used gestational age–specific TSH values.[4] Both, however, are well within ranges reported by others.[14–16] Importantly, as shown in Table 1, maternal demographic characteristics in these women are also similar to those we previously reported.[4] Moreover, pregnancy outcomes as shown in Tables 2 and 3 recapitulate the excessive incidences of preterm labor, placental abruption, and neonatal intensive care unit admissions in women with subclinical hypothyroidism. The additional finding of an increased incidence of diabetes may be explicable by the association of subclinical hypothyroidism with increased maternal age and increased body weight. Several other studies have identified higher TSH and lower T_4 values with increasing body mass index.[17,18] In any case, the currently derived reference range for serum TSH values of 0.08 to 2.99 milliunits/L is valid for detecting adverse pregnancy events in women with subclinical hypothyroidism in the first half of pregnancy.

The demographic characteristics of women with isolated hypothyroxinemia are shown in Table 1. Like women with subclinical hypothyroidism, these women were older, heavier, and more often multiparous when compared with the control cohort. A major finding of this study is that there was no excessive maternal or neonatal morbidity in pregnancies of women identified with isolated hypothyroxinemia when compared with the normal cohort. Specifically, and as shown in Tables 2 and 3, the incidences of preterm delivery, placental abruption, diabetes, and neonatal complications were quite similar. This remained true when gestational age–specific thresholds were used to identify women with isolated hypothyroxinemia. The absence of excessive morbidity in this cohort suggests that isolated maternal hypothyroxinemia, unlike subclinical hypothyroidism, may not be a clinically important finding. Our study, however, does not allow us to directly address any possible adverse effects on neurodevelopment that have been described in children born to pregnant women with isolated hypothyroxinemia.[2,3,19]

Our findings now reported offer an explanation for those recently reported by Cleary-Goldman and colleagues (Cleary-Goldman J, Malone FD, Messerlian G, Sullivan L, Canick J, Porter TF, et al. Subclinical hypothyroidism and pregnancy outcomes [abstract]. Am J Obstet Gynecol 2006;193:S3). They described 10,990 women in whom they determined serum thyrotropin and free thyroxine concentrations in stored serum samples from another investigation. They grouped women together who had either subclinical hypothyroidism or isolated maternal hypothyroxinemia and then determined the prevalence of adverse perinatal outcomes. Except for an association with placental abruption in one subgroup, they found no other excessive adverse outcomes compared with the normal cohort. In view of our findings now reported, we are of the opinion that combining these distinctly different entities likely diluted any significant outcomes associated with subclinical hypothyroidism.

To further elucidate the clinical relevance of isolated hypothyroxinemia during pregnancy, we analyzed thyroid peroxidase (TPO) antibody levels in these 17,298 women. The baseline prevalence of abnormal TPO antibody levels in women with a normal TSH and free T_4 level was 5%. This was quite similar to 4% in women with isolated maternal hypothyroxinemia. By comparison, women with subclinical hypothyroidism had a significantly increased prevalence of these antibodies (31%). These observations are consistent with the conventional view that subclinical hypothyroidism is frequently associated with autoimmune thyroiditis which is a continuum of thyroid failure often preceded by development of TPO antibodies. These findings cast further doubt on the biologic significance of isolated maternal hypothyroxinemia.

Finally, we studied the correlation between serum TSH and free T_4 levels in each of these three groups of pregnant women. As expected, there was a significant negative correlation between these two analytes in women whose values were within the normal reference range (r_s=−0.19, P<.001). As shown in Figure 2B, this significant correlation persisted for women identified with subclinical hypothyroidism (r_s=−0.11, P=.007). These relationships support the concept that thyrotropin elevation usually precedes hypothyroxinemia in the evolution of thyroid failure. To the contrary, however, the correlation between serum thyrotropin and free thyroxine was not significant in women with isolated maternal hypothyroxinemia (Fig. 2A). Although we cannot explain this, it is yet another observation that suggests this may be a laboratory aberration.

When taken together, these findings lead us to conclude that isolated maternal hypothyroxinemia during the first half of pregnancy has no apparent adverse affects on pregnancy outcome. We also conclude that subclinical hypothyroidism can be confidently identified using a more pragmatic single upper TSH threshold.[4] Finally, when prevalence of thyroid peroxidase antibodies and correlations between TSH and free thyroxine levels in women with isolated hypothyroxinemia, subclinical hypothyroidism, or normal thyroid function studies are assessed, we believe that the significance of isolated maternal hypothyroxinemia as a pertinent biologic entity must be questioned. Importantly, there is also currently no evidence that treatment of either isolated hypothyroxinemia or subclinical hypothyroidism during pregnancy results in improved outcomes. Thus, widespread prenatal screening for maternal thyroid disorders is not justifiable at this time. To further evaluate these issues, a randomized, placebo-controlled treatment trial to screen 120,000 pregnant women is being conducted by the Maternal–Fetal Medicine Units Network of the National Institute of Child Health and Human Development.

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