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THYROID FUNCTION IN NEONATES OF WOMEN WITH SUBCLINICAL HYPOTHYROIDISM OR HYPOTHYROXINEMIA

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Abstract

Objective: To assess whether treatment of pregnant women with subclinical hypothyroidism or hypothyroxinemia alters neonatal TSH results.

Study Design: A planned secondary analysis of data from two multi-center randomized, double-masked, placebo-controlled thyroxine replacement trials in pregnant women with either subclinical hypothyroidism or hypothyroxinemia. Infant heel-stick specimens were obtained before discharge. We compared TSH levels between neonates born to mothers allocated to treatment or placebo within each trial and between neonates in the placebo groups. Multiples of means were generated for day-of-life-specific data.

Results: Neonatal TSH values were available for 573/677 (84.6%) newborns from the subclinical hypothyroidism trial and 461/526 (87.6%) newborns from the hypothyroxinemia trial. Neonatal

TSH values did not differ in either trial by treatment group or between placebo groups (P > 0.05 for all comparisons).

Conclusions: Neonatal TSH values did not differ with thyroid hormone replacement in pregnancies diagnosed with subclinical hypothyroidism or hypothyroxinemia.

Precis:

Thyroid hormone replacement in pregnant women with subclinical hypothyroidism or hypothyroxinemia does not significantly affect neonatal TSH values. (18 words)

Keywords

Subclinical hypothyroidism; hypothyroxinemia; pregnancy; neonatal; thyroid function testing

INTRODUCTION:

Overt maternal hypothyroidism, defined by elevated serum thyroid stimulating hormone (TSH) level and decreased free thyroxine (fT4) levels, poses significant risks during pregnancy for both the mother and the fetus. Untreated maternal hypothyroidism has been associated with pregnancy complications including spontaneous abortion, preeclampsia[1–2], preterm birth[3–4], and placental abruption[5]. Associated fetal and pediatric risks include high birth weight[6–7], impaired neuropsychological development[8–9] and death[9]. It is widely recognized that pregnancies complicated by overt hypothyroidism have improved outcomes with treatment that normalizes maternal thyroid function testing, although there remain concerns that these women are still at increased risk for preterm birth and perinatal mortality, particularly if they also have thyroid autoantibodies[10–11].

Overt hypothyroidism complicates 0.2 – 0.3% of pregnancies in the United States[12]. Subclinical hypothyroidism and hypothyroxinemia are substantially more common. They are among the most common endocrine diagnoses in pregnant women in the United States, affecting 2.1[13]-2.5[14]% and 1.3[15]-2.5[16]%, respectively. Both conditions are laboratory diagnoses defined by abnormalities of thyroid function testing. Subclinical hypothyroidism is defined by normal fT4 levels but elevated TSH levels and hypothyroxinemia by low fT4 but normal TSH levels. Over the past several decades considerable controversy has been generated about the impact of these conditions on pregnancy outcomes, with numerous reports that suggest or refute an association of these conditions with various obstetric complications including miscarriage[10,13,17–19], stillbirth[10,18,20], preterm delivery[10–13,17–19,21–24], low birthweight[10,22,24], gestational diabetes[11,13,25–26], gestational hypertension[10,19,22–23,25,27–28], or abruption[10,21,23,24]. The majority of these data are from retrospective cohort studies or small prospective series.

Maternal subclinical hypothyroidism and hypothyroxinemia have been associated with impaired psychomotor development in some retrospective studies[29–30]. However three large clinical trials of thyroid hormone replacement in these conditions have demonstrated no benefit on either perinatal outcomes or on neurodevelopmental outcomes for children[31–32]. The Lazarus trial randomized 794 pregnant women with elevated TSH and/or low fT_4 values to either thyroid hormone replacement or routine clinical care. When evaluated at age 3,

there were no differences in children's IQ scores between the two groups[31]. Casey and colleagues screened almost 100,000 pregnant women for subclinical hypothyroidism or hypothyroxinemia. Participants with either condition were randomized (677 with sublinical hypothyroidism and 526 with hypothyoxinemia) to either thyroid hormone replacement or placebo for the duration of the pregnancy. Children were followed to age 5, at which point testing revealed no differences in IQ testing between treatment and placebo groups in either trial[32].

Despite these findings, it remains uncertain whether treatment of maternal subclinical hypothyroidism or hypothyroxinemia might affect neonatal thyroid function. Some studies have reported a correlation between maternal and neonatal thyroid function studies[29–30,33] while others have shown no correlation[34–35]. This question was clinically relevant during the design of the aforementioned clinical trials, as almost all newborns in the United States now undergo mandated metabolic screening for neonatal thyroid dysfunction. In order to address this uncertainty we performed a planned secondary analysis of two trials of thyroxine therapy for subclinical hypothyroidism or hypothyroxinemia diagnosed during pregnancy[32], with specific attention to the impact of thyroid hormone therapy on neonatal thyroid function testing.

MATERIALS AND METHODS:

This is a planned secondary analysis of data from two *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network clinical trials: Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism, and Randomized Trial of Thyroxine Therapy for Hypothyroxinemia Diagnosed During Pregnancy. These two multi-center studies consisted of randomized, double-masked, placebo-controlled trials of thyroxine replacement in pregnant women diagnosed with either subclinical hypothyroidism (TSH ≥4.0 mU/L and free T4 0.86–1.9 ng/dL) or hypothyroxinemia (TSH 0.08–3.99 mU/L and free T4<0.86 ng/dL) and enrolled between 8 0/7 and 20 6/7 weeks gestation. Women eligible for the primary trials had non-anomalous singleton pregnancies. Exclusion criteria were identical for both trials and included a history of thyroid cancer or current thyroid disease requiring medication, concurrent serious medical illness, planned delivery at a non-Network hospital, inability to commit to a 5-year infant follow-up protocol, and participation in another interventional study that might influence maternal and/or perinatal morbidity and mortality. Participation in these trials in a previous pregnancy was an additional exclusion criterion. Participants had monthly TSH and fT4 assessments during pregnancy, with TSH levels reported for the subclinical hypothyroidism study and fT4 levels for the hypothyroxinemia study. The goal for subclinical hypothyroidism study participants was to attain and maintain a TSH level of 0.1 – 2.4 mU/L. If the TSH level was <0.1 mU/L, the daily dose was reduced by 25 mcg/day. If the TSH level was >2.5 mU/L, the daily dose was increased by 25 mcg/day up to a maximum of 200 mcg/day. The goal for hypothyroxinemia study participants was to attain and maintain a fT4 level of 0.86 – 1.90 ng/dL. If the fT4 level was <0.86 ng/dL, the daily dose was increased by 25 mcg/day up to a maximum of 200 mcg/day. If the fT4 level was >1.90 ng/dL the daily dose was decreased by 25 mcg/day. Sham adjustments were made for participants in the placebo arms. At each monthly visit participants in both studies were asked to bring back

their study drug and any remaining capsules were counted and recorded. New medication was dispensed at the visit. Women requiring dosage adjustments returned to the clinic, ideally within 7 days of the blood draw, to exchange their existing study medications for study capsules corresponding to their new dosage.

Infant heel-stick blood specimens for TSH determination were obtained prior to discharge, generally at 24 to 48 hours after birth as mandated by local metabolic screening regulations. Heel-stick samples were obtained in conjunction with clinically indicated sampling whenever possible. Samples were analyzed in a central laboratory using the fluorescent enzyme immunology methodology widely utilized in clinical neonatal screening programs. We compared neonatal TSH levels between treatment and placebo within each trial. We also compared neonatal TSH levels in the placebo groups between trials.

Because neonatal TSH levels change substantially in the first few days after birth, day-of-life-specific TSH levels from a reference population were used to determine threshold for mean and elevated levels[36]. Multiples of the means were generated based on these data. Elevated TSH levels were defined as >34 μIU/ml for the first 48 hours, and >20 μIU/ml after 48 hours. Categorical variables were compared using the chi-square or Fisher's exact tests, as appropriate, and continuous variables with the Wilcoxon rank sum test.

Because of reported differences in birthweight between infants born of women with overt thyroid disease compared to euthyroid women, we compared birthweights between thyroid replacement and placebo groups in both trials by gestational age, using the small for gestational age (SGA, less than the 10th percentile), appropriate for gestational age (AGA, birth weight 10th to 90th percentile) and large for gestational age (LGA, birth weight greater than the 90th percentile) criteria of Alexander and colleagues[37].

The parent trials were approved by the institutional review boards of all participating clinical centers, and all enrolled women gave written informed consent. The current analysis was approved by the University of Utah Institutional Review Board.

Statistical analysis was conducted with SAS software (SAS Institute, Cary, NC). Nominal P values of less than 0.05 were considered to indicate statistical significance. No adjustments were made for multiple comparisons and there was no imputation for missing data.

RESULTS:

Characteristics of the cohorts analyzed by treatment group are presented in Table 1. Maternal thyroid function testing results were obtained within 40 days of delivery in 559 of 573 women in the subclinical hypothyroidism trial. Of these, 22/273 (8.1%) of active and 88/286 (30.8%) of placebo had subclinical hypothyroidism ($p<0.001$). Of the women in the hyothroxinemia trial 447 of 461 women had thyroid function testing within 40 days of delivery. Of these 108/221 (48.9%) in the active and 169/226 (74.8%) in the placebo had hypothyroxinemia ($p<0.001$).

As previously reported, in the subclinical hypothyroidism trial 93% of women in the levothyroxine group had a thyrotropin level between 0.1 and 2.5 mU/L by a median

gestational age of 21 weeks[32]. In the hypothyroxinemia trial 83% of the women in the levothyroxine group met the treatment goal (fT4 level between 0.86 and 1.90 ng/dL) by a median gestational age of 23 weeks[32].

Neonatal heel stick samples were available for 573/677 (84.6%) newborns from women with subclinical hypothyroidism and 461/526 (87.6%) newborns from women with hypothyroxinemia. These were analyzed for TSH. The most common reasons that neonatal TSH samples were not available were early hospital discharge, stillbirth, and withdrew / lost to follow-up before delivery. Neonatal TSH values, either as median values, multiples of the mean or the frequency of elevated levels, did not differ significantly in either trial based on treatment group (Table 2). There were no differences in TSH values between placebo groups (median [interquartile range] 8.0 [2.5, 15.0] for the subclinical hypothyroidism group and 7.0[2.5,14.0] for the hypothyroxinemia group, p=0.45).

In the subclinical hypothyroidism cohort an association was identified between elevated cord TSH levels and SGA birthweights. This finding was not seen in the hypothyroxinemia cohort (Table 3).

DISCUSSION:

In these large multi-center randomized, double-masked, placebo-controlled trials of thyroid hormone replacement in pregnant women with subclinical hypothyroidism or hypothyroxinemia enrolled between 8 and <21 weeks gestation, neonatal TSH values did not differ with thyroid replacement therapy.

The dramatic changes in thyroid function test results that occur in the first week after birth are well documented. TSH levels rise rapidly after birth, peaking at 60–80 mIU/L within the first hour after delivery. TSH levels then fall over the next few days and after the first week have dropped to approximately 1–8 mIU/L, where they characteristically remain through infancy. Although false-positive TSH screens could be minimized with initial TSH screening at 5–7 days after birth, this is not clinically feasible and the 48-hour time frame, as was used in this study, is now standard practice in most United States jurisdictions.

Although there are a number of prospective and retrospective cohort studies that have reported on obstetric, neonatal and/or neurodevelopmental outcomes in pregnancies complicated by subclinical hypothyroidism or hypothyroxinemia, few have reported on neonatal thyroid testing results. Several have reported a correlation between maternal and neonatal thyroid function studies[29–30,33] while others have shown no correlation[34–35]. Our data, derived from two large concurrent multicenter clinical trials, demonstrate no differences in neonatal TSH values between treated and untreated women with either subclinical hypothyroidism or hypothyroxinemia.

A positive association between cord blood fT4 values and birthweight has been reported[33]. Although we did not measure cord blood fT4, we did examine birthweights in both treatment groups, subdividing them as SGA, AGA, and LGA and by their TSH status (Table 3). Of interest, significantly more newborns with elevated TSH in the subclinical hypothyroidism cohort were SGA. Shields and associates reported a correlation between

elevated fT4 and birthweight but reported no correlation with TSH values[33]. We do not have newborn fT4 values for comparison, which makes our findings difficult to interpret. While a true correlation is possible, this could also represent the impact of unmeasured confounders, particularly environmental exposures, or it may represent a chance statistical association.

Our study does have limitations. As mentioned, we did not measure newborn fT4 or other thyroid hormones other than TSH and are thus unable to assess the newborn's thyroid regulatory system. Likewise, we have measured newborn TSH levels at only a single point in time. TSH measured soon after birth may not reflect thyroid function either in utero or later in life. In addition, we cannot compare these TSH levels to euthyroid controls as all participants in the parent trials had a biochemical abnormality when initially screened.

However, our study also has several strengths. The diagnoses, research interventions, and pediatric follow-up were all precisely defined a priori and carefully monitored in the parent trials. In addition, research TSH samples were obtained primarily in conjunction with mandated neonatal screening samples, making our findings clinically relevant.

We have been unable to demonstrate any effect of thyroid replacement therapy on neonatal TSH values in maternal subclinical hypothyroidism or hypothyroxinemia. Likewise, we found no difference between neonatal TSH values in pregnancies with subclinical hypothyroidism or hypothroxinemia, suggesting that one is not more likely than the other to result in abnormal neonatal laboratory values. While we have demonstrated an association between elevated cord TSH levels and SGA birthweights in the subclinical hypothyroidism cohort, the significance of this finding is unclear.

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Table 1.

Maternal baseline characteristics for those with and without neonatal TSH samples

Characteristic	Subclinical Hypothyroidism			Isolated Hypothyroxinemia		
	Levo-thyroxine N = 282	Placebo N = 291	*P*	Levo-thyroxine N = 231	Placebo N = 230	*P*
Maternal age - year	27.9 ± 5.6	27.6 ± 5.7	0.48	27.9 ± 5.7	28.1 ± 5.7	0.48
Race/Ethnicity - no. (%)			0.97			0.77
Black	21 (7.4)	20 (6.9)		55 (23.8)	58 (25.2)	
Hispanic	154 (54.6)	158 (54.3)		110 (47.6)	103 (44.8)	
White	99 (35.1)	103 (35.4)		62 (26.8)	67 (29.1)	
Other	8 (2.8)	10 (3.4)		4 (1.7)	2 (0.9)	
Maternal BMI kg/m2	28.0 ± 6.4	28.1 ± 6.2	0.57	30.3 ± 6.5	30.1 ± 7.1	0.38
Nulliparous - no. (%)	100 (35.5)	114 (39.2)	0.36	63 (27.3)	54 (23.5)	0.35
Education - no. (%)			0.86			0.76
Less than high school graduate	119 (42.2)	129 (44.3)		99 (42.9)	103 (44.8)	
High school graduate	85 (30.1)	83 (28.5)		97 (42.0)	89 (38.7)	
College graduate	78 (27.7)	79 (27.1)		35 (15.2)	38 (16.5)	
Smoking	13 (4.6)	11 (3.8)	0.62	27 (11.7)	30 (13.0)	0.66
Weeks of gestation at randomization	16.7 ± 2.9	16.8 ± 3.0	0.60	18.0 ± 2.8	17.7± 2.9	0.42

Data presented as mean ± SD, or n (%). Comparisons are for mothers of liveborn infants with and without neonatal TSH samples.

Table 2.

Neonatal TSH values by trial

	Levothyroxine	**Placebo**	***P*-value**
Subclinical Hypothyroidism			
	N = 282	N = 291	
TSH (μIU/ml)	9.0 [2.5, 18.0]	8.0 [2.5, 15.0]	0.11
TSH (Multiple of Mean)	0.9 [0.4, 1.6]	0.8 [0.2, 1.3]	0.06
Age (hours) at time of blood draw	33.9 [23.0, 43.1]	34.2 [23.7, 43.8]	0.63
Elevated TSH (>34 μIU if 1st 48 hrs, >20 μIU if after 48 hrs)[*+]	25/281 (8.9%)	17/286 (5.9%)	0.18
Hypothyroxinemia			
	N = 231	N = 230	
TSH (μIU/ml)	6.0 [2.5, 16.0]	7.0 [2.5, 14.0]	0.64
TSH (Multiple of Mean)	0.6 [0.2, 1.3]	0.7 [0.2, 1.3]	0.47
Age (hours) at time of blood draw	34.4 [24.4, 41.7]	35.8 [24.5, 42.6]	0.40
Elevated TSH (>34 μIU if 1st 48 hrs, >20 μIU if after 48 hrs)[*+]	13/229 (5.7%)	18/228 (7.9%)	0.35

[*] Elevated levels considered a threshold for further neonatal evaluation

[+] Elevated levels could not be calculated when age (hours) at time of blood draw data were missing.

Data presented as median [Interquartile range] or n/total (%)

Table 3.

Association between elevated neonatal TSH values and infant birth weights accounting for gestational age at birth

	Elevated TSH*	Normal TSH	*P*-value
Subclinical Hypothyroidism			
			0.025
SGA (n=50)	8 /50 16.0%	42/50 84.0%	
AGA (n=472)	29/472 6.1%	443/472 93.9%	
LGA (n=45)	5/45 11.1%	40/45 88.9%	
Subclinical Hypothyroxinemia			
			0.16
SGA (n=38)	4 /38 10.5%	34/38 89.5%	
AGA (n=385)	21/385 5.8%	344/385 94.3%	
LGA (n=54)	6/54 11.1%	48/54 88.9%	

SGA, small for gestational age (birth weight less than 10% for gestational age); AGA, appropriate for gestational age (birth weight between 10% and 90% for gestational age); LGA, large for gestational age (birth weight greater than 90% for GA);

*Elevated =TSH (>34 μIU if 1st 48 hrs, >20 μIU if after 48 hrs)