Effects of Increasing Levothyroxine on Pregnancy Outcomes in Women with Uncontrolled Hypothyroidism

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Abstract

Objective—Uncontrolled hypothyroidism has been associated with an increased risk of adverse pregnancy outcomes. We aimed to assess the effectiveness of increasing levothyroxine (LT4) dose on reducing the risk of adverse outcomes for pregnant women with TSH level greater than the recommended 1st trimester limit.

Design, Patients, Measurements—We reviewed the electronic medical records of pregnant women evaluated from January 2011 to December 2013, who had history of LT4-treated hypothyroidism and were found to have TSH > 2.5 mIU/L in 1st trimester. Women were divided into two groups; group A-LT4 dose was increased within 2 weeks from the TSH test, group B-LT4 dose remained stable. We compared the frequency of pregnancy loss (primary outcome) and other pre-specified pregnancy-related adverse outcomes between groups.

Results—There were 85 women in group A (median TSH: 5.0, interquartile range 3.8–6.8 mIU/L) and 11 women in group B (median TSH: 4.5, interquartile range 3.2–4.9 mIU/L). The groups were not different in baseline clinical and socioeconomic characteristics. The mean interval between TSH test and LT4 dose increase was 4.5 (SD 4.6) days. Pregnancy loss was significantly lower in group A (2/85, 2.4%) vs. group B (4/11, 36.4%) (p=0.001). Other pregnancy-related adverse outcomes were similar between groups.

Conclusions—Increasing LT4 dose for women with uncontrolled hypothyroidism in the 1st trimester of pregnancy was associated with a decreased risk of pregnancy loss. Given the limitations of our study, this association awaits further confirmation from larger studies.

Key terms

Hypothyroidism; pregnancy; levothyroxine; thyroid dysfunction; adverse outcomes

Introduction

Primary hypothyroidism affects 3–10% of women[1, 2] and approximately 1–2% of pregnant women receive levothyroxine (LT4) therapy during pregnancy[3]. To meet the challenge of increased metabolic needs during pregnancy, the daily thyroxine requirements could increase up to 50%[4]. These physiologic changes may result in uncontrolled hypothyroidism in women who were euthyroid with appropriate thyroid hormone replacement before pregnancy. In addition, thyroid function test results during pregnancy differ from those of non-pregnant women with TSH concentrations decreasing. Recently, in the absence of a laboratory established TSH reference range during pregnancy, a TSH of 2.5 mIU/L has been accepted as the upper limit of normal in the 1st trimester[5, 6]. Therefore, the recommended treatment of hypothyroidism during pregnancy is with administration of oral LT4 with the goal to normalize maternal serum TSH levels (1st trimester TSH reference range 0.1–2.5 mIU/L)[5, 6].

Overt hypothyroidism in pregnancy has consistently been shown to increase the risk of maternal and fetal complications[7, 8]. Although less frequent than overt, subclinical hypothyroidism during pregnancy has also been associated with adverse events in some studies[8–10], but not consistently[11, 12]. Previous reports have shown that up to 68% of pregnant women on LT4 have an elevated TSH level at their first antenatal visit[13–18]. A recent large study found that the majority of LT4-treated women have early gestational TSH levels above the recommended targets with an increased risk of miscarriage[19]. It has been proposed that pregnant women increase the LT4 dose empirically by 30% on conception to optimize early gestation thyroid function[3, 5, 6, 20].

Our aim was to assess the effectiveness of increasing LT4 dose on reducing the risk of adverse outcomes for LT4-treated hypothyroid pregnant women with TSH level greater than the recommended at the 1st trimester.

Materials and Methods

Subjects

We performed a retrospective cohort study using the electronic medical records of pregnant women between the age of 18 and 45 years, evaluated at Mayo Clinic, Rochester (Olmsted County), MN, USA from January 1, 2011 to December 31, 2013, who had history of LT4-treated hypothyroidism and were found to have TSH > 2.5 mIU/L in their 1st trimester. We included only women with singleton pregnancies, because with multiple pregnancies the higher HCG concentrations result in a downward shift in the TSH reference range compared

to singleton pregnancies[21]. Pregnant women were excluded if free thyroxine (FT4) was checked and was found to be less than 0.8 ng/dL (n=1) or if they were using amiodarone, methimazole, or propylthiouracil (n=1). For the analysis, the cohort was sub-divided into two groups; women whose LT4 dose was increased within 2 weeks from the TSH test (group A) and those whose LT4 dose remained stable (group B). Women who had their LT4 dose increased beyond the 2 weeks were excluded (n= 23). The patients were followed until pregnancy loss or hospital discharge after child delivery. This study was approved by the Institutional Review Board of Mayo Clinic, Rochester, MN, USA.

Study Measures/Assessments

We collected[22] women's baseline characteristics such as age, ethnicity, relationship status, educational level, employment status, and smoking, alcohol, or illicit drug use. For women who were residents of Olmsted County, MN, USA, we calculated the HOUsing-based SES measures index (HOUSES), a validated socioeconomic measure. HOUSES is a composite index that is derived from individual housing features (housing value, square footage, and the number of bedrooms and bathrooms) by linking address information of patients to enumerated real estate property data that is available from the Assessor's Office of local government; higher values represent better socioeconomic status[23]. We also collected information regarding personal history of thyroid disease, diabetes mellitus, hypertension, pregnancy loss, and preterm delivery. We determined if the conception was by assisted reproduction/in vitro fertilization and if the pregnancy was followed in the Maternal Fetal Medicine clinic, which is the Obstetrics clinic for the high-risk pregnancies. At baseline, body mass index (BMI), TSH, FT4, and positivity for TPO antibody were recorded. During follow up, information regarding pregnancy loss (miscarriage/stillbirth), preterm delivery (before 37 weeks), placental abruption, gestational diabetes, gestational hypertension, preeclampsia, eclampsia, premature rupture of membranes (PROM), and intrauterine growth restriction (IUGR) were collected. The birth weight and 5-min Apgar score of the neonates, admission to the neonatal intensive care unit (NICU), and duration of hospital stay after child delivery were recorded. Finally, we recorded any emergency department (ED) visits, hospital admissions, and subsequent TSH testing performed during pregnancy.

Study Procedures

The study cohort was identified using the laboratory data and diagnostic indices provided by Mayo Clinic. We developed a research strategy to identify women who had elevated serum TSH level during pregnancy. Based on the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9), all pregnant women at Mayo Clinic are assigned an ICD-9 code V22.nn (normal pregnancy) or V23.nn (supervision of high-risk pregnancy) at their first clinic visit. We ran a query with serum TSH>2.5 mIU/L ± 100 days (range) from the V22.nn or V23.nn code as well as from 632.nn (missed abortion) and 634.nn (spontaneous abortion). A detailed medical record review was subsequently conducted for all the patients identified through the queries to assess whether they satisfy the inclusion and exclusion criteria.

Assays

During the study period serum TSH was measured using:1) the Hybritech TSH immunoassay (Beckman Coulter D×I 800, Beckman Coulter, Inc. Brea, CA) with inter-assay variation of 4.4–5.8% and intra-assay variation of 3.9–5.6% and 2) the Elecsys immunoassay (Roche Cobas 8000, Roche Diagnostics, Inc. Indianapolis, IN) with inter-assay variation of 2.6–10.9% and intra-assay variation of 0.6–1.9%. FT4 was measured on the ADVIA Centaur platform (Siemens Diagnostics, Inc. Malvern, PA) with inter-assay variation of 7.4–8.3% and intra-assay variation of 1.9–3.4%. TPO antibodies were measured using: 1) the Bayer anti-TPO assay on the ADVIA Centaur platform with inter-assay variation of 5.1–10.2% and intra-assay variation of 1.6–5.2% and 2) the Access TPO antibody immunoassay (Beckman Coulter D×I 800, Beckman Coulter, Inc. Brea, CA) with inter-assay variation of 1.8–14.8% and intra-assay variation of 2.6–6.5%.

Data Analysis

A descriptive summary analysis of patients' baseline characteristics was performed using JMP®10.0.0 (JMP, Cary, NC, USA). Data are presented as frequencies (percentages) for the categorical variables and means (SD; standard deviation) or median (IQR; interquartile range) as appropriate for the continuous variables. Differences between categorical variables were assessed using the chi-square test or Fisher's exact test and between continuous variables using Student's t-test (parametric) or Wilcoxon/Kruskal-Wallis test (non-parametric) as appropriate. Outcomes of interest included: pregnancy loss (primary outcome), preterm delivery, placental abruption, gestational diabetes, gestational hypertension, preeclampsia, eclampsia, PROM, IUGR, low birth weight (LBW; <2500 gr), low 5-min Apgar score (7), NICU admission, neonatal death (restricted to the immediate postpartum period until mother's hospital discharge), and duration of hospital stay. A p-value of <0.05 was considered to be statistically significant and all testing was two-sided.

Results

Baseline characteristics of subjects

During the study period, 96 pregnant women were identified with history of hypothyroidism on LT4 replacement and a TSH > 2.5 mIU/L in their 1st trimester of pregnancy. For 85 women with a median TSH 5 mIU/L (IQR 3.8–6.8 mIU/L), LT4 dose was increased (group A) compared to 11 women with median TSH 4.5 mIU/L (IQR 3.2–4.9 mIU/L) whose LT4 dose remained stable (group B). The mean gestational age at the time of TSH testing was 7.2 (SD 2.3) weeks for group A and 6.8 (SD 2.7) weeks for group B (p=0.59). The mean interval between TSH test and LT4 dose increase was 4.5 (SD 4.6) days. Group A had an initial mean LT4 dose of 129.4 (SD 43.8) mcg which was subsequently increased on average 27.5% (SD 11.4%). The mean LT4 dose for group B was 90.8 (SD 30.0) mcg. The distribution of different types of thyroid disease between the two groups is described in Table 1. Baseline characteristics were no different between groups (Table 2). No pregnant woman reported illicit drug use. Four patients had history of type 1 diabetes and one patient had history of hypertension, all in group A.

Nine pregnancies (11%) were conceived by assisted reproduction/in vitro in group A compared to none in group B (p=0.59). Finally, similar number of patients was followed in the Maternal Fetal Medicine clinic (group A; n=2, 2.4%, group B; n=0, 0%, p=0.99).

Pregnancy important outcomes and follow-up

Table 3 describes the adverse outcomes between the two groups. Pregnancy loss was significantly lower in group A (2/85, 2.4%) vs. group B (4/11, 36.4%) (p=0.001). Table 4 describes the cases of pregnancy loss. There was no reported cause of the pregnancy losses in the medical records. Only one patient from group A had a repeated TSH testing prior to the pregnancy loss which was at goal (2.1 mIU/L). None of the patients in group B had a repeated TSH testing prior to the pregnancy loss. We performed a sensitivity analysis by excluding the two cases from group B that pregnancy loss occurred within 1 week from the TSH testing as any LT4 dose change would have been unlikely to have impact on the outcome. Pregnancy loss remained significantly lower in group A (2/85, 2.4%) vs. group B (2/9, 22.2%) (p=0.04).

There was no significant difference between the two groups in the frequency of: preterm delivery, gestational diabetes, gestational hypertension, pre-eclampsia, placenta previa, placenta abruption, low birth weight, or Apgar 7 at 5 min. Thirteen women in group A (15.3%) had PROM compared to none in group B (p=0.35). No pregnant woman developed eclampsia or had IUGR. There were no events of congenital malformations or neonatal death. The mean duration of the hospital stay was 2.6 (SD 1.0) days for group A, similar with group B at 3.0 (SD 1.2) days (p=0.36).

After initiating LT4, 35 pregnant women in group A had a repeat TSH testing while there were still in the 1st trimester with 17 women having achieved TSH at goal (17/35, 49%). By the second trimester 93% of pregnant women in group A had a TSH at goal. Two women achieved TSH at goal only in the 3rd trimester; 1 of them had PROM. Finally, 3 women never achieved TSH at goal; 1 of them had PROM and subsequent preterm delivery. The median percentage of trimester-specific TSH level at goal was 75% (IQR 62–100%). The median TSH level was 1.3 mIU/L (IQR 0.8–2.1 mIU/L) at the last testing before the end of pregnancy.

From the 7 remaining pregnant women in group B, 5 had spontaneously a TSH level at goal at the second testing (2/5 were still in the 1st trimester and 3/5 were in the 2nd trimester) and 2 at the third testing during pregnancy (both women in the 2nd trimester); therefore LT4 dose remained stable. The median TSH level was 2.4 mIU/L (IQR 2.2–2.8 mIU/L) at the last testing before the end of pregnancy.

One patient from group A was recorded to have palpitations; however her TSH level was at goal. There was no difference between groups regarding the number of ED visits or hospital admissions during pregnancy (data not shown). A Caesarian delivery was performed for 30/84 (36%) of women in group A and 4/7 (57%) in group B. Complete follow up was available for all patients.

Discussion

In this single-center study, 96 LT4-treated pregnant women with uncontrolled hypothyroidism in their 1st trimester of pregnancy were identified. An association of increasing LT4 dose with decreased risk of pregnancy loss was found, however, there was no apparent effect on other important adverse maternal or fetal outcomes. This suggests that once the critical stage of the 1st trimester of pregnancy has been completed, the chances of an uncomplicated pregnancy would be appreciable for issues associated with hypothyroidism. It has been previously described that LT4 requirements plateau by week 16 of gestation[3]. This may contribute to the success of the patients who had a stable LT4 dose in achieving eventually TSH normalization and having similar risk for late-pregnancy complications with the patients who had their LT4 dose increased at the beginning of pregnancy.

A recent population-based study[19] showed that among 1,013 LT4-treated women, 63% had in their 1st trimester a TSH level above the recommended goal of 2.5 mIU/L. Compared to LT4-treated women with TSH levels within the current guidelines (0.2–2.5 mIU/L), women with TSH greater than 2.5 mIU/L in the 1st trimester had an increased risk of miscarriage after adjusting for age, year of pregnancy, diabetes, and socioeconomic characteristics. The risk of miscarriage was increased in women with TSH 4.51–10 mIU/L [odds ratio (OR) 1.80, 95% confidence interval (CI) 1.03, 3.14)] and TSH greater than 10 mIU/L (OR 3.95, 95% CI 1.87, 8.37).

Similarly, Abalovich et al.[24] showed that when treatment with levothyroxine was inadequate, pregnancy loss occurred in 60% of overtly hypothyroid patients and in 71.4% of patients with subclinical hypothyroidism, whereas when treatment was adequate, 100% of overtly hypothyroid patients and 90.5% of patients with subclinical hypothyroidism carried the pregnancies to term. Hallengren et al[15] found that fetal loss was significantly greater in pregnant women with TSH value above 4.0 mIU/L (5/19, 26%) compared to those with normal TSH values (2/32, 6%). From a biologic standpoint, these findings are supported by human studies suggesting that adequate thyroid hormonal availability is important at the level of placental trophoblasts[25]. Therefore, inadequate treatment may have caused the pregnancy losses for the women in group B and possibly for the one woman in group A as there was no documentation of TSH normalization after her levothyroxine dose was increased.

This body of evidence underlines the need for a strict and early follow up in pregnancy of women with treated hypothyroidism. Close treatment monitoring will allow detecting the need for increases in the LT4 dose in most patients during pregnancy. Though no prospective, randomized investigation of LT4 intervention has occurred in hypothyroid pregnant women, such an investigation would be unethical and prohibitive to complete. Despite the small sample size, our study is the largest to date reporting on adverse pregnancy outcomes of women with LT4-treated uncontrolled hypothyroidism that LT4 dose was increased compared to those that was not, allowing us to show the effectiveness of increasing LT4 dose in the 1st trimester on reducing the risk of pregnancy loss. This finding supports the current clinical practice guidelines that recommend LT4-treated hypothyroid

patients who are newly pregnant should independently increase their dose of LT4 by approximately 25%–30% upon a missed menstrual cycle or positive home pregnancy test and notify their caregiver promptly[5]. However, this increase might be insufficient, as it has been observed in the study by Verga et al[26] where patients needed to increase their LT4 dose from 45% to 70%. Therefore, it has been suggested that to best achieve normal TSH levels early, during the first trimester, the thyroid status on LT4 needs to be optimized even before the patient becomes pregnant[27].

The main limitation of our study is its retrospective design, which results in no randomization of the patients to balance their prognosis. In addition, there is also a risk of selection bias due to physicians being more likely to intensify the treatment for patients considered at higher risk for complications; this bias, however, would strengthen the findings of benefit. This is a single-center study including mostly Caucasian, well-educated pregnant women; therefore the results may not be applicable to the general population. Although the presence of referral bias cannot be excluded, the number of pregnant women followed in the Maternal Fetal Medicine clinic suggesting a high-risk pregnancy was small and similar between the two groups. In addition, there may be some non-apparent clinical differences in the etiology of the pregnancy loss. Finally, many of the secondary adverse pregnancy outcomes are uncommon and differences between groups may not have been possible to detect due to our sample size. The low number of women and events also affects the main analysis, likely underestimating the p-value associated with the observed differences. Although it would have been clinically meaningful, we were not able to perform analysis based on a TSH cut-off level due to the small size of those subgroups. However, an important strength of our study is the use of electronic medical records capturing detailed clinical data which in combination with the fact that we had complete follow up of our subjects allowed us to have a complete outcome assessment. Finally, we had data on multiple potential confounders, most notably socioeconomic measures and obstetric comorbid conditions.

In conclusion, increasing LT4 dose to improve the adequacy of thyroid hormone replacement for uncontrolled hypothyroidism during pregnancy was associated with a decreased risk of pregnancy loss. Given the limitations of our study, this association awaits confirmation in larger studies that will also establish the optimal TSH target during pregnancy.

Acknowledgments

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Table 1

Types of thyroid disease in pregnant women with hypothyroidism

	Group A-LT4 increased n=85 n (%)	Group B-LT4 stable n=11 n (%)
Hashimotos's thyroiditis	58 (68)	10 (91)
Graves' disease (treated)	12* (14)	0 (0)
Thyroid nodule	1 (1)	0 (0)
Thyroid cancer	2 (2)	0 (0)
Other/Unknown	12 (14)	1 (9)

LT4; Levothyroxine therapy

*
9 patients were treated with radioactive iodine, 2 patients had thyroidectomy, and 1 patient had no documentation of the definitive treatment

Table 2

Baseline characteristics of pregnant women with hypothyroidism

	Group A-LT4 increased (n=85)	Group B-LT4 stable (n=11)	*P*-value
Clinical Characteristics			
Age, mean (SD), years	31 (4.2)	30 (5.5)	0.71
BMI, median (IQR), kg/m^2	26 (23–31)	27(22–36)	0.53
TSH, median (IQR), mIU/L	5 (3.8–6.8)	4.5 (3.2–4.9)	0.06
TPO-ab +, n (%) [*]	36/54 (67)	5/11 (71)	0.99
Hx pregnancy loss, n (%)	24 (28)	2 (18)	0.72
Hx preterm delivery, n (%)	4 (5)	0 (0)	0.99
Smoking, n (%)	2 (2)	1 (9)	0.31
Alcohol, n (%)	2 (2)	0 (0)	0.99
Socioeconomic Characteristics			
Married/Committed relationship, n (%)	75 (88)	9 (82)	0.62
Employed, n (%)	72 (85)	10 (91)	0.99
College+, n (%)	77 (91)	10 (91)	0.99
HOUSES z-score, mean (SD)	−0.8 (2.6) [**]	−0.3 (2.6) [**]	0.60
Race			0.62
Caucasian, n (%)	73 (86)	11 (100)	
Asian, n (%)	5 (5.8)	0 (0)	
African-American, n (%)	3 (3.5)	0 (0)	
Unknown/Other, n (%)	4 (4.7)	0 (0)	

LT4; Levothyroxine therapy, BMI; body mass index, TSH; thyroid stimulating hormone, TPO-ab; thyroperoxidase antibody, Hx; history, college+; at least some college or 2-year degree

[*] Available in 68% of the cohort

[**] Group A, n=55 and Group B, n=8

Table 3

Adverse outcomes of pregnant women with hypothyroidism

Maternal Outcomes, n (%)	Group A-LT4 increased (n=85)	Group B-LT4 stable (n=11)	*P*-value
Pregnancy loss	2 (2.4)	4 (36.4)	0.001
Preterm delivery (< 37 weeks)	7 (8.2)	0 (0)	0.99
Gestational diabetes	5 (5.9)	1 (9.1)	0.53
Gestational hypertension	5 (5.9)	0 (0)	0.99
Pre-eclampsia	2 (2.4)	0 (0)	0.99
Premature rupture of membranes	13 (15.3)	0 (0)	0.35
Placenta previa	1 (1.2)	0 (0)	0.99
Placenta abruption	2 (2.4)	0 (0)	0.99
Neonatal Outcomes, n (%)	Group A-LT4 increased (n=83)	Group B-LT4 stable (n=7)	*P*-value
NICU admission	2 (2.4)	0 (0)	0.99
Birth weight < 2500gr	3 (3.6)	0 (0)	0.99
Apgar 7 at 5 min	3 (3.6)	0 (0)	0.99

LT4; Levothyroxine, NICU; neonatal intensive care unit

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Table 4

Pregnancy loss events

CASES	Pregnancy loss gw	Maternal age (yr)	Maternal comorbidities*	TSH (mIU/L)	TSH gw	LT4 dose increase gw
Group A-LT4 increased						
1	15.9	30	h/o miscarriage	3.1	7.4	8.3
2	11.6	40	h/o miscarriage	5.4	7.0	7.9
Group B-LT4 stable						
1	8.6	24	none	3.4	6.7	NA
2	7.1	28	none	3.2	6.1	NA
3	7.9	40	none	4.9	3.7	NA
4	6.0	19	tobacco use	3.9	5.0	NA

LT4; Levothyroxine therapy, TSH; thyroid stimulating hormone, gw; gestational week, yr; years, h/o; history of

*
Includes: h/o miscarriage, diabetes, hypertension, autoimmune diseases, tobacco/alcohol/drug use