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Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women with Subclinical Hypothyroidism

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Background: Subclinical hypothyroidism (SCH) has been associated with increased risk of adverse pregnancy outcomes in some, but not all, studies. Uncertainty remains regarding the impact of levothyroxine (LT4) therapy on improving health outcomes in pregnant women with SCH. The objective of this study was to assess the potential benefits of LT4 therapy in pregnant women with SCH.
Methods: The medical records were reviewed of pregnant women with SCH, defined as an elevated serum thyrotropin (TSH) of >2.5 mIU/L for the 1st trimester or >3 mIU/L for the 2nd and 3rd trimesters, but ≤10 mIU/L. Pregnant women were divided into two groups depending on whether they received LT4 (group A) or not (group B). Pregnancy loss and other pre-specified adverse outcomes were evaluated during follow-up.
Results: There were 82 women in group A and 284 in group B. Group A had a higher body mass index ($p = 0.04$) and a higher serum TSH level ($p < 0.0001$) compared with group B. Group A had fewer pregnancies lost ($n = 5$ [6.1%] vs. $n = 25$ [8.8%]; $p = 0.12$), low birth weight (LBW) offspring (1.3% vs. 10%; $p < 0.001$), and no neonates with a five-minute Apgar score ≤7 (0% vs. 7%; $p < 0.001$) compared with group B. Other pregnancy-related adverse outcomes were similar between the two groups. Inferences remained unchanged after considering different models to adjust for potential predictors of outcome.
Conclusions: LT4 therapy is associated with a decreased risk of LBW and a low Apgar score among women with SCH. This association awaits confirmation in randomized trials before the widespread use of LT4 therapy in pregnant women with SCH.

Introduction

Subclinical hypothyroidism (SCH) is a biochemical diagnosis based on a high serum thyrotropin (TSH) level with a normal free thyroxine (fT4) level. Current guidelines recommend an upper serum TSH limit of 2.5 mIU/L for the first trimester and 3.0 mIU/L for the second and third trimesters of pregnancy (1). Multiple observational studies comparing euthyroid pregnant women to those with untreated SCH have found an association of SCH with an increase in the risk of one or more adverse pregnancy outcomes, most commonly pregnancy loss, preterm delivery, gestational hypertension, and low birth weight (LBW) (2–6). However, other studies did not find any association of SCH with pregnancy complications (7–10). Publication bias may have affected these reports, as negative studies are less likely to be published. Moreover, the vast majority of the studies assessing the impact of SCH in pregnancy are at low to moderate risk of bias, warranting less confidence in their results due to small samples, imprecision in the estimates, and failure to adjust for confounding factors (11,12).

Despite the paucity of strong supportive data, the American Thyroid Association 2011 guidelines recommended levothyroxine (LT4) therapy for pregnant women with SCH and positive thyroperoxidase (TPO) antibody status (1), while the Endocrine Society in 2012 recommended LT4 therapy for all pregnant women with SCH (13). However, uncertainty remains regarding the impact of LT4 therapy on improving health outcomes in pregnant women with SCH. Taking into consideration recent studies presenting a prevalence of SCH up to 15% in the United States (14) and 28% in China (15), millions of pregnant women worldwide will be

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treated with LT4 based on current recommendations. To date, there are no data from randomized trials or other intervention studies documenting benefit from LT4 therapy in this population. To address this knowledge gap, a large single-center study was performed to estimate the potential benefits of LT4 therapy in pregnant women with SCH.

Materials and Methods

Subjects

A retrospective cohort study was performed using the electronic medical records of pregnant women aged between 18 and 45 years, evaluated at the Mayo Clinic (Rochester, MN) from January 2011 to December 2013 who met the criteria for SCH. SCH during pregnancy was defined as serum TSH >2.5 mIU/L for the 1st trimester or >3 mIU/L for the 2nd and 3rd trimesters, but ≤10 mIU/L. TSH was checked following clinical practice guidelines for screening of thyroid dysfunction through a case-finding approach. This period was chosen to allow enough duration of follow-up to assess the outcomes of interest. This period also covers an interval prior to and after the release of the recommendation for LT4 therapy from the medical societies. This coverage should allow pregnant women to be captured who were less likely to receive LT4 therapy (prior to publication of the guidelines) or who were more likely to receive LT4 therapy (after publication of the guidelines) based on clinical practice patterns rather than patient characteristics. Women with singleton pregnancies were included because, with multiple pregnancies, the higher human chorionic gonadotropin concentrations result in a downward shift in the TSH reference range compared with singleton pregnancies (16). The plan was to exclude women if fT4 was checked and was found to be low (<0.8 ng/dL), but no such cases were identified. Subjects using medications affecting thyroid function (thyroid hormone preparations, amiodarone, methimazole, and propylthiouracil) were also excluded. For analysis, the cohort was subdivided into two groups: women who had been started on LT4 therapy (group A), and those who had not (group B). The participants were followed until pregnancy loss or hospital discharge after child delivery. This study was approved by the Institutional Review Board of the Mayo Clinic (Rochester, MN).

Study measures/assessments

An electronic data collection form was created using REDCap (17), and a standardized data dictionary defining each variable to be collected was followed. Prior to proceeding to independent record review, a group of records ($n = 5$) was reviewed for calibration across reviewers, which showed 100% agreement. Baseline characteristics such as age, race/ethnicity, relationship status, educational level, employment status, and smoking/alcohol/illicit drug use were collected. For women who were residents of Olmsted County, MN, the team 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 property data that are available from the Assessor's Office of local government; higher values represent better socioeconomic status (18). Information regarding personal history of thyroid disease (not on thyroid hormone therapy), diabetes mellitus, hypertension, pregnancy loss, and preterm delivery was also collected. Further, it was determined if the conception was by assisted reproduction/*in vitro* fertilization and if the patient was followed in the Maternal Fetal Medicine clinic, which is the obstetrics clinic for 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 five-minute Apgar score of each neonate, admission to the neonatal intensive care unit (NICU), and duration of hospital stay after child delivery were recorded. Finally, any emergency department (ED) visits, hospital admissions, and subsequent TSH testing performed during pregnancy were recorded. One researcher (S.M.) assessed a random sample (5% of the cases) to verify accuracy, finding 99% agreement between reviewers when evaluating inclusion criteria and 99% agreement when evaluating adequate outcome assessment.

Study procedures

The study cohort was identified using the laboratory data and diagnostic indexes provided by the Mayo Clinic. A research strategy was developed to identify women who had elevated serum TSH levels during pregnancy. Based on the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9), all pregnant women at the 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. A query was run with serum TSH >2.5 mIU/L ± 100 days (range) from the V22.nn or V23.nn code. The rationale of expanding the search to 100 days prior to the ICD-9 code assignment was to ensure that pregnant women who had their TSH checked before the clinic visit were not missed. It is possible that pregnant women could have a miscarriage before receiving a V22.nn or V23.nn code. Given that the primary outcome is pregnancy loss and to make sure these women were not missed, a query was run with serum TSH >2.5 mIU/L ± 100 days from the ICD-9 codes 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 satisfied the inclusion and exclusion criteria.

Assays

During the study period, serum TSH was measured using: (i) the Hybritech TSH immunoassay (Beckman Coulter DxI 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 (ii) 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: (i) 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 (ii) the Access TPO antibody immunoassay (Beckman Coulter DxI 800; Beckman Coulter, Inc.), 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). Data are presented as frequencies (percentages) for the categorical variables and means ± standard deviation (*SD*) or median (interquartile range [IQR]) as appropriate for the continuous variables. Differences between categorical variables were assessed using the chi-square 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, LBW (<2500 g), low five-minute Apgar score (≤7), NICU admission, neonatal death (restricted to the immediate postpartum period until mother's hospital discharge), and duration of hospital stay. A multivariate logistic regression model was also performed to assess the association of LT4 therapy with adverse pregnancy outcomes, controlling for potential confounders (TSH, BMI, education) when there was an adequate number of events. For the outcomes of pregnancy loss and preterm delivery, the plan was also to control for history of pregnancy loss and history of preterm delivery, respectively, as these are strong predictors for a future event. Results are reported as odds ratios (OR) and confidence intervals (CI), with group A being the reference group. A *p*-value of <0.05 was considered to be statistically significant, and all testing was two-sided.

Results

Baseline characteristics of subjects

For the period January 2011 to December 2013, 366 pregnant women with SCH were identified retrospectively. Eighty-two women were started on LT4 therapy (group A) compared with 284 women who did not receive any LT4 therapy (group B). It was found that 17.7% (23/130) of pregnant women with SCH were treated in 2011, 19.8% (24/121) in 2012, and 30.4% (35/115) in 2013. Baseline characteristics of the two groups can be found in Table 1. The groups were not different with regard to age, race/ethnicity, history of pregnancy loss or preterm delivery, smoking, alcohol, and illicit drug use during pregnancy. The groups were similar in terms of socioeconomic characteristics, education, relationship status, employments status, and HOUSES z-score. Group A had a higher mean BMI compared with group B (29 ± 7.7 kg/m^2 vs. 27 ± 6.6 kg/m^2; $p = 0.04$) and a higher mean serum TSH level (4.9 ± 1.4 mIU/L vs. 3.5 ± 0.9 mIU/L; $p < 0.0001$). The median gestational age at the time of TSH testing was 7.1 weeks (IQR 6.3–9.1 weeks) for group A and 7.6 weeks (IQR 6.3–10 weeks) for group B. More patients in group A ($n = 17$; 21%) had a history of thyroid disease (Hashimoto's thyroiditis, thyroid nodularity, or unspecified) compared with group B ($n = 20$; 7%; $p < 0.001$). The number of pregnancies conceived by assisted reproduction/*in vitro* fertilization was similar between the two groups (group A: $n = 4$, 4.9%; group B: $n = 9$, 3.2%; $p = 0.50$). Finally, a similar number of patients was followed in the Maternal Fetal Medicine clinic (group A: $n = 6$, 7.3%; group B: $n = 24$, 8.5%; $p = 0.74$).

Table 1. Baseline Characteristics of Pregnant Women with Subclinical Hypothyroidism

	Group A (LT4), n = *82*	*Group B (no LT4),* n = *284*	p-*Value*
Clinical characteristics			
Age, *M* (*SD*), years	30 (5.2)	30 (4.5)	0.78
BMI, *M* (*SD*), kg/m^2	29 (7.7)	27 (6.6)	0.04
TSH, *M* (*SD*), mIU/L	4.9 (1.4)	3.5 (0.9)	<0.0001
TPO-Ab+, *n* (%)[a]	19/41 (46)	14/48 (29)	0.09
Hx thyroid disease, *n* (%)	17 (21)	20 (7)	<0.001
Hx pregnancy loss, *n* (%)	24 (29)	62 (22)	0.17
Hx preterm delivery, *n* (%)	7 (9)	18 (6)	0.50
Smoking, *n* (%)	3 (3.7)	17 (6)	0.39
Alcohol, *n* (%)	2 (2.4)	1 (0.4)	0.13
Illicit drugs, *n* (%)	0 (0)	1 (0.4)	0.99
Diabetes, *n* (%)	2 (2.4)	3 (1.1)	0.31
Hypertension, *n* (%)	0 (0)	4 (1.4)	0.58
Socioeconomic characteristics			
Married/committed relationship, *n* (%)	64 (78)	225 (79)	0.82
Employed, *n* (%)	72 (88)	228 (80)	0.11
College+, *n* (%)	73 (89)	253 (89)	0.92
HOUSES z-score, *M* (*SD*)	–0.36 (3.27)[b]	0.23 (3.62)[b]	0.33
Race/ethnicity			0.31
Caucasian, *n* (%)	77 (94)	244 (86)	
Hispanic, *n* (%)	0 (0)	5 (1.8)	
Asian, *n* (%)	1 (1.2)	15 (5.3)	
African American, *n* (%)	2 (2.4)	11 (3.9)	
Unknown/other, *n* (%)	2 (2.4)	9 (3.2)	

[a]Available in 24% of the cohort.
[b]Group A, $n = 43$; Group B, $n = 176$.
LT4, levothyroxine therapy; *SD*, standard deviation; BMI, body mass index; TSH, thyrotropin; TPO-Ab, thyroperoxidase antibody; Hx, history; College+, at least some college or two-year degree; M, mean.

Follow-up

The median gestational age for LT4 initiation was 9.1 weeks (IQR 7.7–11.5 weeks). Group A had on average 2.5 ± 1.6 additional TSH checks during pregnancy compared with 0.2 ± 0.5 for group B. The median percentage of trimester-specific TSH level at goal was 80% (IQR 50–100%) for patients in group A. Only 44 (15.5%) women in group B had repeat TSH testing during pregnancy; 31 had an improved TSH level within the normal trimester-specific reference range, nine had an improved TSH level but still higher than the normal trimester-specific reference range, and four had a worse TSH level. One patient in group A developed an asymptomatic serum TSH suppression (TSH 0.09 mIU/L) requiring a decrease of LT4 dose. There was no difference between groups with regard to the number of ED visits or hospital admissions during pregnancy (data not shown). Specifically for group A, none of the patients was recorded to have tachycardia. The frequency of cesarean section was similar between the two groups (group A: 28.2%; group B:

Table 2. Characteristics of Patients with Pregnancy Loss

	Pregnancy loss, n = *30*	*No pregnancy loss,* n = *336*	p-*Value*
Age, median (IQR), years	30 (28–37)	30 (27–33)	0.18
BMI, median (IQR), kg/m^2	25 (22–30)	25 (22–30)	0.94
TSH, median (IQR), mIU/L	3.4 (2.8–4.3)	3.4 (3.0–4.1)	0.97
TPO-Ab+, *n* (%)[a]	2/10 (20)	31/79 (39)	0.31
Hx pregnancy loss, *n* (%)	4 (13.3)	82 (24.4)	0.26
College+, *n* (%)	29 (97)	297 (89)	0.23
HOUSES z-score, *M* (*SD*)	0.66 (4.72)[b]	0.05 (3.40)[b]	0.44

[a]Available in 24% of the cohort.
[b]"Pregnancy loss" group, $n = 23$; "No pregnancy loss" group, $n = 123$.
IQR, interquartile range; HOUSES, HOUsing-based SES measures index; M, mean.

23.5%; $p = 0.40$). After delivery or pregnancy loss, 38/82 (46%) of the women treated with LT4 continued on treatment, whereas 44/82 (54%) discontinued treatment. Complete follow-up was available for all patients.

Pregnancy outcomes

There were 30 pregnancy losses in the cohort (24 miscarriages and 6 stillborn). Pregnancy loss was lower in group A ($n = 5$; 6.1%) compared with group B ($n = 25$; 8.8%), but that difference was not statistically significant ($p = 0.12$). Table 2 shows the characteristics of the women who experienced a pregnancy loss compared with those who did not. Overall, the two groups did not seem to differ in terms of important risk factors for pregnancy loss.

Group A had fewer LBW offspring (1.3% vs. 10%; $p < 0.001$) compared with group B. It was found that women who were not started on LT4 therapy were 16.4 times more likely to deliver babies with LBW compared with those who received treatment (OR 16.4 [CI 2.7–326.9]). The majority ($n = 21/27$; 78%) of LBW offspring were delivered preterm ($p < 0.0001$). There was also a significant decrease in the frequency of a low Apgar score in the neonates of group A compared with group B (0% vs. 7%; $p < 0.001$). Although not statistically different, women in group B were less likely to have gestational hypertension (OR 0.64 [CI 0.23–1.93]) and PROM (OR 0.71 [CI 0.29–1.79]) compared with group A. The mean duration of the hospital stay was 2.5 ± 0.9 days for group A, which was similar to group B at 2.7 ± 2.1 days. There was no significant difference between the two groups in other maternal and neonatal outcomes. No pregnant woman developed eclampsia. A comparison between the two groups for all adverse outcomes can be found in Table 3. A sensitivity analysis was performed using the multivariate

Table 3. Adverse Pregnancy Outcomes of Patients with Subclinical Hypothyroidism

Maternal outcomes, n *(%)*	*Group A (LT4),* n = *82*	*Group B (no LT4),* n = *284*	*OR*	*CI*	p-*Value*	*Variables*[a]
Pregnancy loss	5 (6.1)	25 (8.8)	2.44	0.80–8.87	0.12	TSH, education, Hx pregnancy loss
Preterm delivery (<37 weeks)[c]	4 (4.9)	30 (10.6)	3.06	0.96–12.28	0.06	TSH, education, Hx preterm delivery
Gestational diabetes	3 (3.7)	24 (8.5)	3.31	0.91–16.57	0.07	TSH, education, BMI
Gestational hypertension	8 (9.8)	19 (6.7)	0.64	0.23–1.93	0.42	TSH, education, BMI
Pre-eclampsia	2 (2.4)	10 (3.5)	3.37	0.66–26.84	0.15	TSH, BMI
Premature rupture of membranes	10 (12.2)	28 (9.9)	0.71	0.29–1.79	0.44	TSH, education, BMI
Intrauterine growth restriction[b]	1 (1.2)	5 (1.8)	1.45	0.23–28.1	0.99	
Placenta previa[b]	0 (0)	3 (1.1)		NA	0.99	
Placenta abruption[b]	0 (0)	1 (0.4)		NA	0.99	
Neonatal outcomes, n *(%)*	*Group A (LT4),* n = *77*	*Group B (no LT4),* n = *259*	*OR*	*CI*	p-*Value*	*Variables*[a]
NICU admission	2 (2.6)	10 (3.9)	1.94	0.38–15.36	0.45	TSH
Birth weight <2500 g	1 (1.3)	26 (10)	16.4	2.7–326.9	<0.001	TSH, education, BMI
Apgar ≤7 at 5 minutes	0 (0)	18 (7)		NA	<0.001	TSH, education
Neonatal death[b]	0 (0)	4 (1.5)		NA	0.58	
Congenital malformations[b]	0 (0)	4 (1.5)		NA	0.58	

Group A is the reference group.
[a]Variables included in the multivariate analysis.
[b]Not enough events to perform a multivariate analysis.
[c]Preterm delivery <34 weeks accounted for 1/4 preterm deliveries in group A and 11/30 preterm deliveries in group B.
NICU, neonatal intensive care unit.

model in which the variable of education was replaced with the HOUSES z-score as a measure of socioeconomic status, and similar findings were obtained (data not shown). The distribution of adverse outcomes was also assessed between the treated patients who had a TSH level ≤3 mIU/L (at goal) during the second half of pregnancy (>20th gestational week) and those who had a TSH level >3 mIU/L (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/thy).

Discussion

A single-center study was performed to evaluate important adverse patient outcomes in pregnant women with SCH. A cohort of 366 pregnant women with SCH was identified who were on average young and overweight. This is the largest cohort reporting pregnancy outcomes of women with SCH who were treated with LT4 therapy compared with those who were just observed. An association of LT4 therapy with decreased risk in LBW and low Apgar score was found. However, no difference in pregnancy loss or other maternal and neonatal outcomes was found.

In 2013, a Cochrane systematic review on interventions for SCH during pregnancy did not identify any studies evaluating the effectiveness of LT4 therapy on maternal and neonatal outcomes, and concluded that there are insufficient data to make recommendations for clinical practice (19). Since that publication, there are still no clinical trials evaluating the impact of LT4 therapy on pregnancy-related outcomes in women with SCH.

One large randomized study designed to compare ''universal screening'' with ''case finding'' methods in detecting thyroid dysfunction provides indirect evidence for the effectiveness of LT4 therapy in preventing adverse pregnancy outcomes (20). Hypothyroid pregnant women who were found to have a serum TSH >2.5 mIU/L and positive TPO antibody levels were started on LT4. Given that there was no upper TSH cutoff level and normal fT4 level was not an inclusion criterion, this study by design allowed the inclusion of pregnant women with overt hypothyroidism, who are at higher risk for adverse pregnancy and neonatal outcomes. The study found that the proportion of hypothyroid women with at least one adverse obstetrical or neonatal outcome was significantly higher in the low-risk ''case finding'' group (not diagnosed and thus untreated; 91%) compared with the low-risk ''universal screening'' group (diagnosed and treated; 34%), suggesting a benefit from LT4 therapy.

A prospective study in China screened women in the first trimester of pregnancy for thyroid dysfunction (21). Women with SCH were recommended LT4 therapy, but only 14% of the study population proceeded with treatment. The study found an increased risk of pregnancy loss in pregnant women with untreated SCH compared with euthyroid pregnant women (relative risk [RR] 1.75 [CI 1.12–2.73]). However, comparing 28 pregnant women with SCH who received LT4 therapy to 168 women who did not receive treatment, the study did not find any difference in the rates of pregnancy loss (RR 0.46 [CI 0.12–1.84]), preterm delivery (RR 0.31 [CI 0.02–5.13]), gestational hypertension (RR 3.00 [CI 0.28–31.99]), LBW (RR 0.65 [CI 0.04–11.71]), or low Apgar score (RR 0.65 [CI 0.04–11.71]). This study was at high risk of bias, most importantly selection bias, had a small sample size and number of events leading to imprecision, and failed to correct for covariates of pregnancy risk.

As far as the impact of hypothyroidism treatment on children's cognitive function is concerned, a multicenter randomized trial assessed the effects of LT4 therapy on the intelligence quotient (IQ) of children born to women who had serum TSH >97.5th percentile or fT4 < 2.5th percentile, or both, during pregnancy (22). A *post hoc* analysis for the subgroup of pregnant women who met the criteria for SCH (elevated serum TSH with normal fT4 levels) found that the treatment had no effect on the mean offspring IQ at three years, or the proportion of children with IQ <85, although LT4 could have been initiated too late in pregnancy to be effective.

Based on the evaluation of this evidence, the American Thyroid Association and the Endocrine Society recommend LT4 therapy for pregnant women with SCH. This study found that although there was around a twofold increase in the number of pregnant women who received LT4 replacement therapy for SCH after the release of the updated guidelines, these recommendations have not been universally implemented. It is believed that this is related in part to the paucity of strong supportive data of such recommendations, as well as the limited penetration guidelines have in various specialty groups. While the results of ongoing trials in this field are awaited, the present results support LT4 therapy without identifying any evidence of harm. However, the possibility of overtreatment in pregnancy still cannot be excluded (23). Therefore, clinicians and pregnant women with SCH need to have a frank discussion regarding the potential benefits of LT4 therapy while taking into consideration the burden of treatment (i.e., daily pills, frequent tests, healthcare visits) and each woman's values and preferences (24). Future studies should include women with additional comorbidities or with multiple gestations, as these are higher-risk subpopulations that have not been adequately studied. Moreover, similar to the recommendations for LT4 therapy when TSH is >10 mIU/L in adults with SCH who are not pregnant, it is important to establish if a similar treatment threshold exists for pregnant women with SCH—a level of TSH above which treatment is likely to induce benefit.

The main limitation of this study is its retrospective, observational 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 offer treatment to patients considered at higher risk for complications. 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. The definition of SCH was modified, as normal fT4 was not used as an inclusion criterion. The reason behind this is that in clinical practice, fT4 is not routinely checked in pregnant women (14), partly due to the limitations of the available assays, and the elevated TSH level is used to guide treatment. Similarly, a very small subset of the cohort had TPO antibody levels measured, which did not allow a subgroup analysis by TPO antibody positivity to be done. Finally, many adverse pregnancy outcomes are uncommon, and differences between groups may not have been possible to detect with the sample size. For example, although it would have been clinically meaningful, it was not possible to perform a

subgroup analysis based on a TSH cutoff level due to the small size of those subgroups. However, this study is the largest to date reporting on pregnancy outcomes of women with SCH who were treated with LT4 compared with those were not, allowing a greater number of adverse events to be identified and showing differences between groups regarding certain outcomes. Another strength of this study is the use of electronic medical records capturing detailed clinical data, combined with the fact that complete follow-up of the subjects allowed for a complete outcome assessment. Finally, data were available on multiple potential confounders, most notably socioeconomic measures and obstetric comorbid conditions, enabling the analyses to be adjusted appropriately.

In conclusion, LT4 therapy is associated with a decreased risk in LBW and low Apgar score. This association may not be causal and awaits confirmation in randomized trials before deciding on the widespread use of LT4 therapy in pregnant women with SCH.

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Author Disclosure Statement

The authors have nothing to disclose.

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