THYROID
Volume 31, Number 5, 2021
Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2020.0609

Thyroid Laboratory Testing and Management in Women on Thyroid Replacement Before Pregnancy and Associated Pregnancy Outcomes

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Background: Women with hypothyroidism before pregnancy often require an increase in their levothyroxine dosage to maintain a euthyroid state during pregnancy. The objectives of this study were to investigate: (i) the frequency and distribution of thyrotropin (TSH) testing and levothyroxine dosage adjustment by gestational age, (ii) the magnitude of levothyroxine increase by the underlying etiology of hypothyroidism, and (iii) the relationship of overtreatment or undertreatment during pregnancy with adverse pregnancy outcomes among women using thyroid replacement before pregnancy.

Methods: A retrospective cohort study of pregnancies in women on thyroid replacement before pregnancy in Alberta, Canada, was performed. Women using thyroid replacement anytime during the two years before pregnancy who delivered between October 2014 and September 2017 were included. Delivery records, physician billing, and laboratory and pharmacy administrative data were linked. Outcomes included characteristics of TSH testing, levothyroxine dosing, and pregnancy outcomes. The frequency and gestational timing of TSH testing and levothyroxine adjustments were calculated. Multiple logistic regression was used to test whether pregnancies with TSH <0.10 mIU/L (overtreatment) or TSH ≥10.00 mIU/L (undertreatment) compared with control pregnancies (TSH 0.10–4.00 mIU/L) were associated with adverse pregnancy and neonatal outcomes.

Results: Of the 10,680 deliveries, 8774 (82.2%) underwent TSH testing at least once during pregnancy, at a median gestational age of six weeks. An adjustment of levothyroxine dosage was made for 4321 (43.7%) during pregnancy. TSH in pregnancy below 0.10 mIU/L increased the odds of preterm delivery when compared with control pregnancies (adjusted odds ratio, 2.14 [95% confidence interval 1.51–2.78]). TSH ≥10.00 mIU/L during pregnancy was not associated with any adverse pregnancy or neonatal outcomes in the multivariable analysis.

Conclusions: Although most women on thyroid replacement before conception had TSH measured at some point during pregnancy, it is concerning that 17.8% did not. Levothyroxine overtreatment in pregnancy was associated with preterm delivery. These findings suggest that clinicians should be careful to avoid overtreatment with levothyroxine in pregnancy.

Keywords: pregnancy, thyroid and pregnancy, thyroid function tests, hypothyroidism, pregnancy outcomes, overtreatment

Introduction

Hypothyroidism affects 2–6% of reproductive-age and pregnant women (1–3). Physiologic changes to thyroid homeostasis occur in pregnancy, and result in an increase in thyroxine (T4) requirements to maintain a euthyroid state (4–9). Women with inadequate thyroid reserves before pregnancy may be unable to adequately meet this increased demand. As a result, an estimated 50–85% of women with hypothyroidism preceding conception require an increase in levothyroxine dosage throughout pregnancy (5,9–12). In addition, the magnitude of thyroid hormone increase appears

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to depend on the underlying etiology of hypothyroidism (7,11). Overt hypothyroidism has been associated with adverse pregnancy outcomes (4). Optimizing levothyroxine dosage in pregnant women with preexisting hypothyroidism prevents the development of overt hypothyroidism in pregnancy (13).

Epidemiologic studies have found that between 20% and 60% of women on thyroid replacement therapy have elevated thyrotropin (TSH) at presentation to their first prenatal visit (12,14–18). The 2017 American Thyroid Association (ATA) pregnancy guidelines strongly recommend that, among hypothyroid women contemplating pregnancy, levothyroxine should be adjusted preconception to achieve a TSH level of less than 2.50 mIU/L and should be increased by 25–30% as soon as pregnancy is confirmed to prevent TSH elevation in the first trimester (4). There are little data examining the relationship between suboptimal levothyroxine treatment and pregnancy outcomes in women receiving thyroid replacement before conception. In particular, the potential adverse effects of overtreatment caused by aggressive empiric increases in thyroid hormone among women receiving preconception levothyroxine have not be well studied.

The aim of this study is to describe the current management patterns of thyroid hormone testing and treatment among pregnant women who were on thyroid hormone preconception and to evaluate the relationship between TSH levels achieved throughout pregnancy and pregnancy outcomes.

Methods

Study design and population

Administrative data were collected retrospectively on females aged 15 to 49 years, who delivered in Alberta, Canada, between October 1, 2014, and September 30, 2017. Women were included in the study if they had filled a prescription for any thyroid replacement medication (levothyroxine, desiccated thyroid, or liothyronine) in the two years before conception.

Ethics approval was obtained from the Conjoint Health Research Ethics Board, University of Calgary (REB18-0223). The analysis plans and protocol were registered in Open Science Framework before viewing any of the data.

Data sources

Deliveries were identified through the Alberta Perinatal Health Program (APHP) database. The APHP database comprises provincial delivery records for all hospital and registered midwife-attended home births in Alberta from 20 weeks' gestation (19).

Using the unique maternal personal health care number, data were linked to the Discharge Abstract Database (DAD) for hospitalization data, to the province-wide laboratory databases from Alberta Health, Alberta Health Services (AHS), and Alberta Precision Laboratories, to the Pharmaceutical Information Network (PIN) database for details on prescription medications, and to physician claims for outpatient physician visits from Alberta Health. Obstetrical and neonatal outcomes were collected through the APHP database and DAD data from Data and Analytics, AHS.

Definitions and outcome measures

The normal reference range for TSH in pregnancy was defined as 0.10–4.00 mIU/L, based on the 2017 ATA guidelines (4). Mean TSH measurements taken up to four months preconception were included in the preconception analysis of TSH value distribution. Frequency of TSH testing in pregnancy was analyzed according to trimesters (first trimester from conception to 12 weeks 6 days' gestation, second trimester from 13 to 27 weeks 6 days' gestation, and third trimester from 28 weeks to term).

A dosage adjustment was defined as a change in dispensed levothyroxine dosage from the preconception period to anytime in pregnancy. The magnitude of increase in levothyroxine dosage during pregnancy was assessed among women who had at least one dosage change during pregnancy. Women were excluded from all analyses related to levothyroxine dosage if they had filled prescriptions for two different daily doses of levothyroxine on the same day, due the inability to accurately determine their dosage because instructions written on the prescription provided are not available in the PIN database. Thus, filling two different daily doses of levothyroxine on the same day could mean that patients were either using a combination of dosages or taking different dosages on different days. Levothyroxine dosage postpartum was defined by the prescription dosage filled for thyroid medication after delivery within the first year postpartum.

The magnitude of levothyroxine dosage adjustments made during pregnancy was analyzed by the underlying etiology of hypothyroidism. Women were divided into one of the following categories, according to their International Classification of Diseases (ICD)-10 and/or ICD-9 billing codes for thyroid disease, where available: (i) primary hypothyroidism (ICD-9 244.9, 245.0–245.2 and/or ICD-10 E03.2, E03.3; E06.0-E06.9); (ii) hypothyroidism resulting from treated Graves' disease, either from ablation or surgery (ICD-9 242.0, 244.1, 242.9 and/or ICD-10 E05.0, E05.8, E05.9); (iii) hypothyroidism following surgery for thyroid cancer (ICD-9 193 and/or ICD-10 C73); and (iv) congenital hypothyroidism (ICD-9 243 and/or ICD-10 E03.0–E03.1). Women without available billing codes were excluded from the analyses about diagnostic categories.

The associations between over- or undertreatment of pregnant women and pregnancy outcomes were examined. In the prespecified analysis plan, the undertreatment group included females who had at least one TSH ≥10.00 mIU/L during pregnancy and the overtreatment group comprised those who had at least one TSH <0.10 mIU/L at any time in pregnancy. TSH ≥10.00 mIU/L was prespecified for the definition of the undertreatment group to maximize the ability to find a clinically meaningful difference.

Statistical analyses

Descriptive statistics were used to calculate the proportion of women with thyroid function testing during pregnancy and the frequency of each specific thyroid test. Data were compared using t-tests for continuous variables where appropriate and chi-squared tests for categorical variables. Repeated-measures analysis of variance was used to examine changes in dosages from preconception over the course of the pregnancy for the entire cohort, as well as for each diagnostic subgroup. Univariate and multivariable analyses were

performed using multiple logistic regression to test whether being overtreated (TSH <0.10 mIU/L) or undertreated (TSH ≥10.00 mIU/L) was independently associated with pregnancy outcomes. A *p*-value of <0.05 was considered statistically significant. Analyses were performed using SPSS (IBM SPSS Statistics, Version 25, 20186).

Results

Among 202,900 deliveries between October 1, 2014, and September 30, 2017, in Alberta, Canada, 10,680 deliveries (5.3%) were from women on thyroid hormone before conception (Fig. 1). Demographics of the cohort are provided in Supplementary Table S1.

TSH testing during pregnancy

Of the 10,680 pregnancies, 8774 (82.2%) had at least one TSH measurement (Fig. 1) and 6707 (62.8%) had at least two TSH tests during pregnancy. A total of 6161 pregnancies (57.7%) had at least one TSH test performed in the first trimester (Fig. 1). In addition, 1737 (16.2%) had a free T4, 11 (0.1%) had a total T4, 34 (0.3%) had a free triiodothyronine, and 932 (8.7%) had TPO antibodies measured at some point during pregnancy. We also performed a supplementary analysis restricted to women who had filled at least two prescriptions for thyroid hormone replacement before conception and found similar results: 9297 women filled two or more prescriptions for thyroid replacement in the two years before conception and 7698 (82.8%) of them underwent TSH testing at least once during pregnancy.

In women who had at least one TSH measurement during pregnancy, the mean ± SD number of tests performed was 1.1 ± 1.0 in the first trimester, 1.4 ± 1.2 in the second trimester, 0.9 ± 0.9 in the third trimester, and 3.4 ± 2.3 over the entire pregnancy. The median gestational age for first and second TSH measurements was 6 weeks (interquartile range [IQR] 4–11) and 14 weeks (IQR 9–22), respectively. The distribution of TSH values preconception and during pregnancy is summarized in Table 1.

TSH testing preconception

A total of 4741 (44.4%) pregnancies had at least one TSH measured in the four months before conception. The preconception TSH measurement was in the range of 0.10–4.00 mIU/L in 3129 (66.0%) of those pregnancies (Table 1). When the range for TSH as recommended by the ATA guidelines (0.1–2.5 mIU/L) was used, a total of 2067 (43.6%) pregnancies had a TSH in this range.

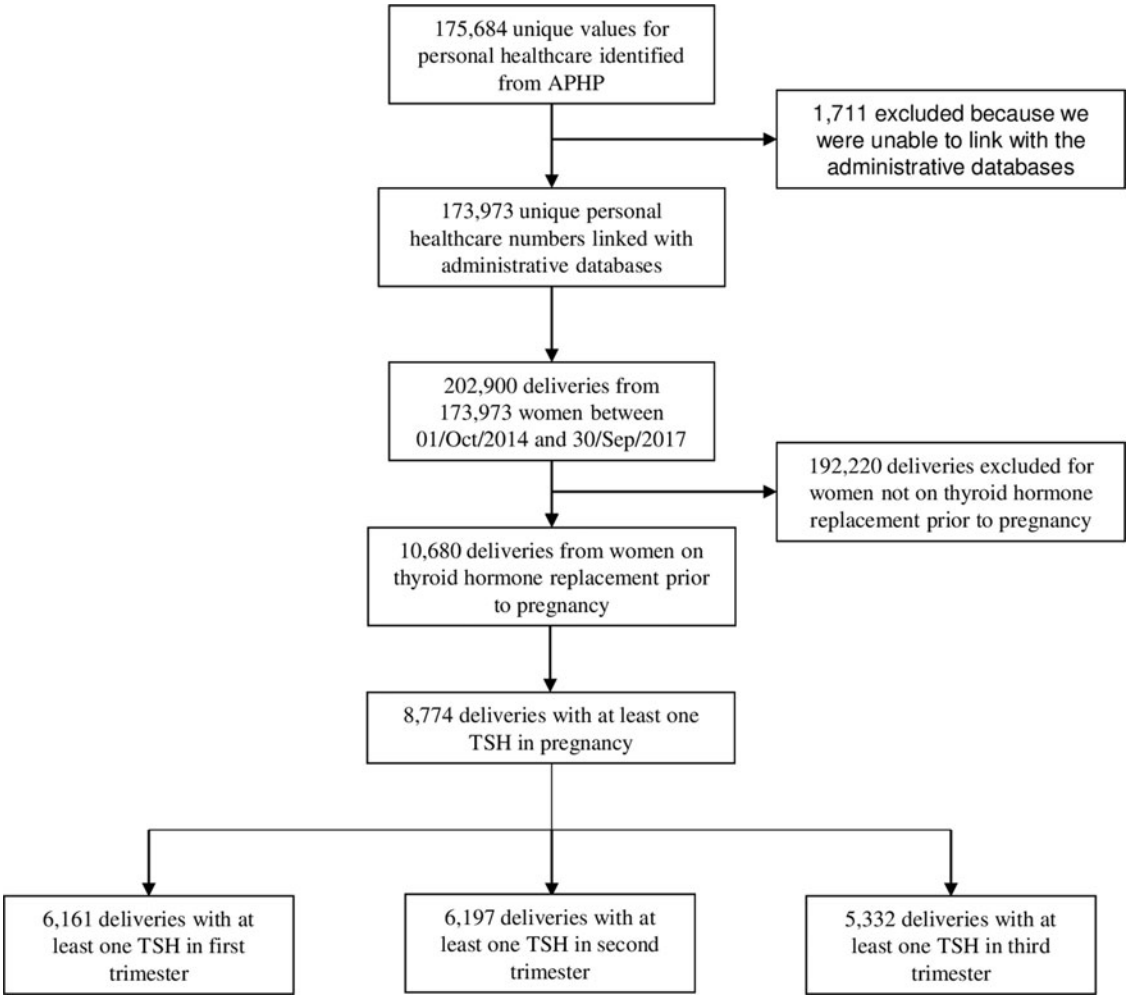

FIG. 1. Flow diagram of derivation of the study population. APHP, Alberta Perinatal Health Program; TSH, thyrotropin.

Table 1. Distribution of Thyrotropin Measurements Before Conception and During Pregnancy

TSH value (mIU/L)	*<0.10*	*≥0.10 to ≤2.50*	*>2.50 to ≤4.00*	*>4.00 to <10.00*	*≥10.00*	*Total*
TSH before conception (up to four months)	189 (4.0%)	2067 (43.6%)	1062 (22.4%)	1153 (24.3%)	270 (5.7%)	4741 (100%)
First TSH in pregnancy	240 (2.7%)	4078 (46.5%)	2129 (24.2%)	1725 (19.7%)	602 (6.9%)	8774 (100%)
Highest TSH value in pregnancy	53 (5.9%)	3062 (34.9%)	2468 (28.1%)	2306 (26.2%)	885 (10.1%)	8774 (100%)

TSH, thyrotropin.

T4 dosage and adjustments in pregnancy

Among the cohort of 10,680 pregnancies from women on thyroid replacement therapy before conception, 325 pregnancies were excluded from the levothyroxine dosage and adjustment analysis, as these women were treated either with liothyronine or thyroid gland preparation, or both. A total of 486 pregnancies were further excluded due to the inability to accurately determine levothyroxine dosage, resulting in 9869 pregnancies available for analysis of levothyroxine dosage in pregnancy.

Of 9869 pregnancies, a total of 4321 (43.7%) had at least one adjustment in levothyroxine dosage during pregnancy. Of those, the mean ± SD number of levothyroxine dosage adjustments was 0.9 ± 0.7 in the first trimester, 0.9 ± 0.8 in the second trimester, 0.5 ± 0.7 in the third trimester, and 2.3 ± 1.2 over the entire pregnancy. The median gestational age for the first dosage adjustment was 10 weeks (IQR 5–19) and the most common timing was gestational weeks 5 and 6. A total of 1056 pregnancies had a single dosage adjustment during pregnancy, 1510 had two dosage adjustments, and 1755 had more than two dosage adjustments. Preconception, trimester-specific, and postpartum daily levothyroxine dosage distributions in women who had at least one dosage adjustment during pregnancy are shown in Figure 2. Levothyroxine dosage significantly increased as pregnancy progressed and fell postpartum ($F(3, 4315) = 1288.1$, $p < 0.001$). The mean and median absolute increase in levothyroxine dosages was 27 and 24 mcg/day throughout the pregnancy. Overall, among pregnancies that had at least one dose adjustment, the median cumulative increases in levothyroxine were 17.9%, 35.7%, and 43.6%, in the first, second, and third trimesters, respectively, compared with the preconception levothyroxine dosage. Among pregnancies with at least one TSH measurement >4.00 mIU/L, 71.5% had at least one levothyroxine dose adjustment during pregnancy.

Levothyroxine dosing by diagnosis

A total of 4973 pregnancies had diagnostic billing codes available to determine the etiology that resulted in the use of thyroid replacement. These pregnancies were categorized as follows: primary hypothyroidism, treated Graves' disease, thyroid cancer, or congenital hypothyroidism (Supplementary Fig. S1). Analyses of levothyroxine dosage throughout pregnancy were carried out for each diagnostic group and are presented in Figure 3. There was a significant increase in

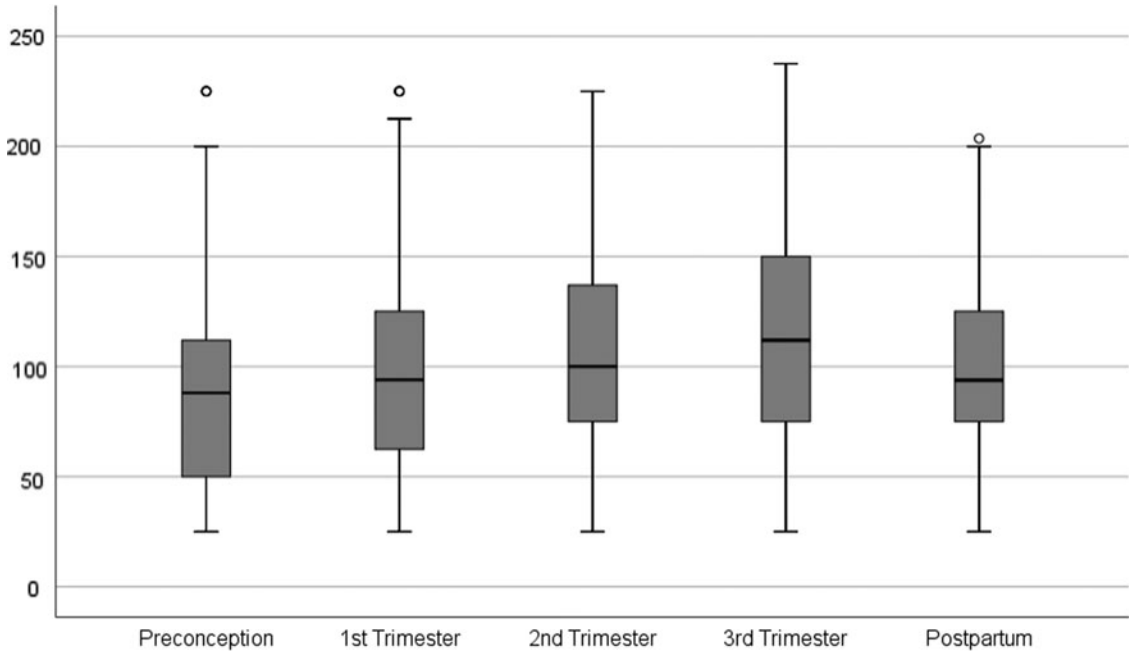

FIG. 2. Levothyroxine daily dosing distribution, prior, during, and after pregnancy, in pregnancies with at least one dose adjustment (X axis). The y axis represents daily levothyroxine dose in micrograms. The central box represents the values from the lower to upper quartile (25th–75th percentile). The middle line represents the median and the whiskers extent from the minimum to maximum values, excluding the ''outliers'' values, which are individually displayed as circles.

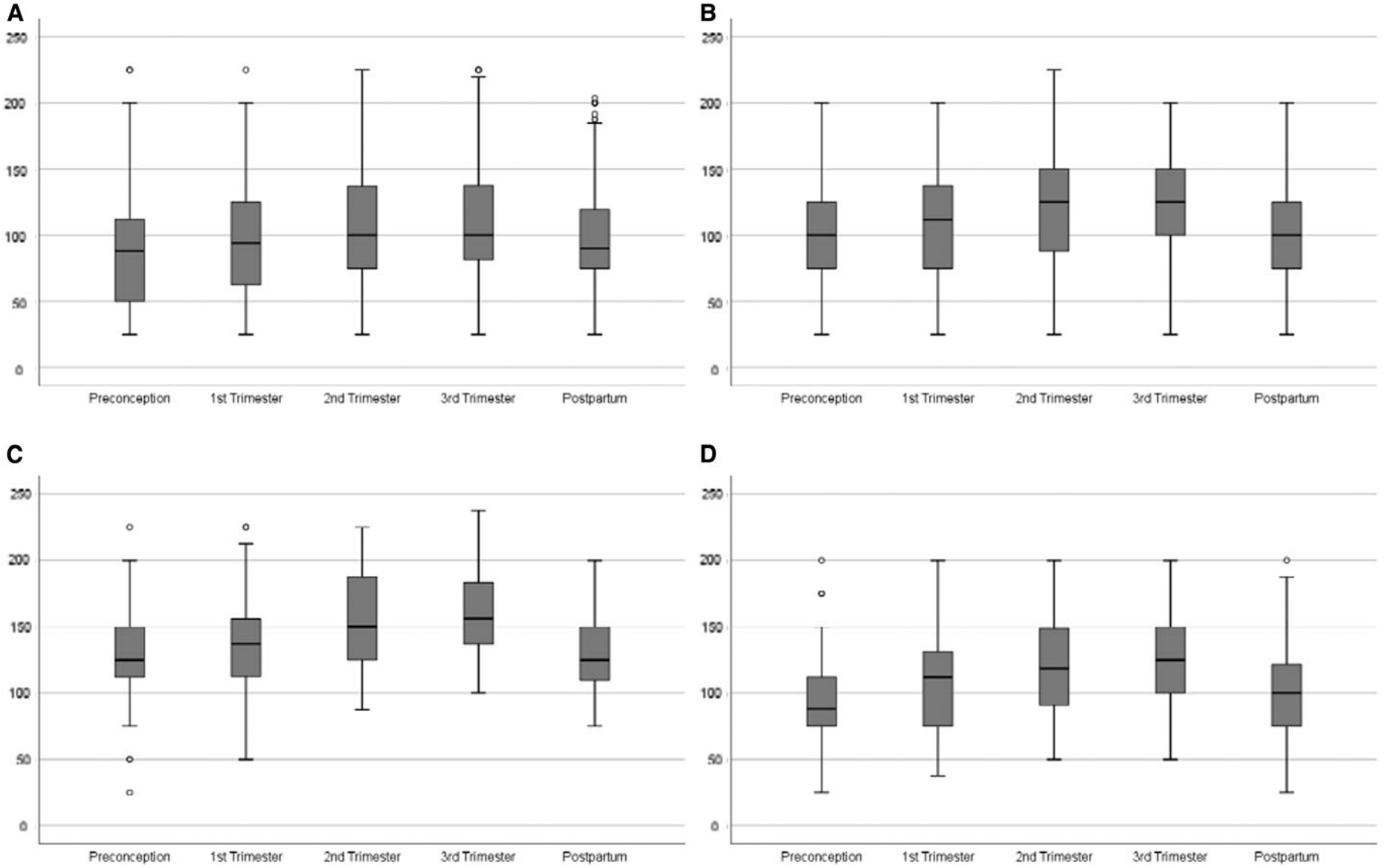

FIG. 3. Levothyroxine daily dosing distribution, prior, during, and after pregnancy, in pregnancies with at least one dose adjustment (X axis). The y axis represents daily levothyroxine dose in micrograms. (**A**) Primary hypothyroidism. (**B**) Hypothyroidism resulting from treated Graves' disease. (**C**) Hypothyroidism following surgery for thyroid cancer. (**D**) Congenital hypothyroidism.

levothyroxine dosage during pregnancy and a reduction in dosage after delivery (F (3,2427) = 130.65, $p < 0.001$). This pattern was consistent among all diagnostic groups and no between-group differences were observed with regard to evolution in thyroid replacement dosing over time ($F(9,5906) = 1.21$, $p = 0.28$). The four subgroups had significantly different dosages throughout pregnancy (F (3, 2429) = 41.28, $p < 0.001$), and *post hoc* comparisons using the Scheffe test showed that the thyroid cancer group had significantly higher dosages compared with the other three diagnostic groups (all *p*-values were <0.001).

Pregnancy and neonatal outcomes

Among 8774 pregnancies with TSH testing performed during pregnancy, 351 pregnancies (4.0%) had at least one TSH measurement <0.10 mIU/L, whereas 797 pregnancies (9.1%) had at least one TSH measurement ≥10.00 mU/L. Pregnancies with TSH 0.10–4.00 mIU/L ($n = 5225$) were used as the control group for comparison of clinical outcomes. Data for pregnancy and neonatal outcomes were missing for seven pregnancies (0.1%). A total of 88 pregnancies (1.0%) met the criteria for both overtreatment and undertreatment and were excluded from these analyses. No associations were observed between overtreatment or undertreatment groups and preeclampsia, gestational hypertension, gestational diabetes, postpartum hemorrhage, venous thromboembolic events, and large for gestational age and small for gestational age infants (Table 2). Preterm delivery was more common in the overtreatment group than that in the control group (16.5% vs. 8.2%; unadjusted odds ratio [OR] 2.21; 95% confidence interval [CI 1.64–2.98]) and the association remained statistically significant after adjustment for confounders (adjusted OR 2.14 [CI 1.51–2.78]) (Table 2). In the univariate analysis, neonatal intensive care unit admission was more common in both the overtreatment and the undertreatment groups compared with the control group (unadjusted OR 1.92 [CI 1.39–2.64] and 1.36 [CI 1.06–1.74]). However, those associations were no longer apparent after adjustment for potential confounders (adjusted OR 1.24 [CI 0.94–2.09] and 1.24 [CI 0.93–1.55]) for the overtreatment group and undertreatment group, respectively (Table 2). A *post hoc* analysis excluding 34 pregnancies with a diagnostic billing code for thyroid cancer from the overtreatment group was carried out and demonstrated the same findings after adjustment for confounders (data not shown). Furthermore, a sensitivity analysis was performed to evaluate pregnancy and neonatal outcomes in 2306 pregnancies with at least one TSH measurement in the range of 4.01–9.99 mIU/L, defined as the mild undertreatment group (Table 2). In the univariate analyses, preeclampsia, gestational hypertension, preterm delivery, and neonatal intensive care unit admission were slightly more common in the mild undertreatment compared with the control group. However, none of these associations remained significant after adjustment for confounders in the multivariable analyses.

An additional sensitivity analysis restricted to women who had filled at least two prescriptions for thyroid hormone replacement before conception was performed (Supplementary Table S2). Compared with the original cohort, results remained unchanged in the adjusted analyses except that the association between overtreatment and neonatal intensive care unit admission reached statistical significance (adjusted OR 1.49 [CI 1.03–2.16]).

A *post hoc* analysis was performed to identify characteristics associated with TSH <0.10 mIU/L during pregnancy (Supplementary Table S3). The likelihood of having a TSH <0.10 mIU/L during pregnancy was increased when the closest TSH measurement to conception was <1.50 mIU/L or the levothyroxine dosage was at least 100 mcg/day in the 12 months before conception ($p < 0.001$). Furthermore, pregnancies with a diagnosis of thyroid cancer or treated Graves' disease had a greater likelihood of TSH suppression, while those with a diagnosis of primary hypothyroidism were less likely to be overtreated.

Discussion

This study demonstrated that although the majority (82.2%) of pregnancies in women on thyroid replacement predating pregnancy had TSH testing at least once during pregnancy, it is concerning that a sizeable proportion (17.8%) did not. Most of the TSH measurements (70.2%) occurred in the first trimester. When first tested in pregnancy, the TSH value was greater than or equal to 10.00 mIU/L in 6.9% of pregnancies. An adjustment in levothyroxine dosage was made for 43.7% of pregnancies at some point during pregnancy. The majority of pregnancies that had levothyroxine titrated during pregnancy received two or more adjustments. The data suggested a potential harm of overtreating pregnant women on thyroid replacement, as a TSH level below 0.10 mIU/L at any time during pregnancy was associated with a doubling of the odds of preterm delivery.

It is well recognized that titration of levothyroxine dose is often required during pregnancy in women with preexisting thyroid disease to replicate normal physiologic changes and maintain a normal TSH, although the optimal management strategy is not established. This study demonstrated that the most common timing for first levothyroxine dose adjustment in pregnancy was around five to six weeks of gestation. Among women who had at least one adjustment in thyroid hormone dosage during gestation, the median cumulative increase in levothyroxine from preconception to third trimester was 44%, consistent with previously published data (5,9).

The cohort in this study included pregnancies between 2014 and 2017. The ATA guidelines from 2011 and 2017 recommend that pregnant women on levothyroxine before conception should immediately increase their levothyroxine by two additional tablets a week at the time of conception, representing an approximate dosage increase of 30% (4,20). The efficacy and safety of this approach have been investigated in a prospective study in which women with treated hypothyroidism were randomized to increase levothyroxine by either two or three tablets per week once pregnant (13). Both interventions prevented TSH elevations in the first trimester, but resulted in TSH suppression below 0.10 mIU/L in 8% and 26% of women, in the two- and three-tablet increase groups, respectively. Observational studies have highlighted the association between overt hypothyroidism and adverse pregnancy complications, as well as negative childhood neurocognitive outcomes (10,14,21,22). However, there is paucity of information on the relationship between overtreatment with levothyroxine and potential effects on pregnancy outcomes. A community-based study published by

Table 2. Obstetrical and Neonatal Outcomes in Overtreatment, Overt Undertreatment, Mild Undertreatment, and Control Groups During Pregnancy

	Control group (TSH 0.10–4.00 mIU/L)	*Overtreatment group (TSH <0.10 mIU/L anytime during pregnancy)*			*Overt undertreatment group (TSH ≥ 10 mIU/L anytime during pregnancy)*			*Mild undertreatment group (TSH 4.01–9.99 mIU/L anytime during pregnancy)*		
	n = *5225*	n = *351*	*Unadjusted OR [CI]*	*Adjusted OR [CI]*	n = *797*	*Unadjusted OR [CI]*	*Adjusted OR [CI]*	n = *2306*	*Unadjusted OR [CI]*	*Adjusted OR [CI]*
Preeclampsia	53 (1.0)	<5	0.83 [0.26–2.66]		8 (1.0)	0.97 [0.46–2.05]		39 (1.7)	**1.68 [1.11–2.55]**	1.55 [0.96–2.53][a]
Gestational hypertension	331 (6.4)	31 (8.8)	1.41 [0.96–2.07]		61 (7.7)	1.20 [0.91–1.60]		186 (8.1)	**1.30 [1.08–1.56]**	1.20 [0.99–1.48][a]
Gestational diabetes	566 (11.0)	40 (11.4)	1.04 [0.74–1.46]		81 (10.2)	0.91 [0.72–1.17]		275 (11.9)	1.12 [0.96–1.30]	
Venous thrombosis in peripartum	<5	0 (0)	1.00 [1.00–1.00]		0 (0)	1.00 [1.00–1.00]		<5	0.76 [0.08–7.26]	
Postpartum hemorrhage	449 (8.7)	36 (10.3)	1.19 [0.83–1.71]		81 (10.2)	1.18 [0.92–1.52]		199 (8.6)	1.00 [0.84–1.20]	
Preterm delivery[b]	422 (8.2)	58 (16.5)	**2.21 [1.64–2.98]**	**2.14 [1.51–2.78]**[c]	81 (10.2)	1.26 [0.98–1.62]		244 (10.6)	**1.35 [1.14–1.59]**	1.13 [0.94–1.38][c]
NICU admission >24 hours	401 (7.8)	49 (14.0)	**1.92 [1.39–2.64]**	1.24 [0.94–2.09][a]	82 (10.3)	**1.36 [1.06–1.74]**	1.24 [0.93–1.55][a]	222 (9.7)	**1.28 [1.08–1.52]**	1.16 [0.98–1.45][a]
LGA[d]	476 (9.3)	38 (10.8)	1.19 [0.84–1.69]		79 (9.9)	1.08 [0.84–1.39]		223 (9.7)	1.07 [0.90–1.26]	
SGA[d]	275 (5.4)	20 (5.7)	1.07 [0.67–1.71]		42 (5.3)	0.98 [0.71–1.37]		127 (5.5)	1.05 [0.85–1.30]	

Bold values indicate association reach statistical significance.

Data are presented as counts (%).

Control group was used as the referent group.

[a]Adjusted for maternal age, smoking status, hypertension, diabetes, obesity, socioeconomic status, and gestational age at delivery. Socioeconomic status was based on maternal deprivation index, derived from postal code (24).

[b]Preterm delivery defined as delivery <37 weeks.

[c]Adjusted for maternal age, smoking status, hypertension, diabetes, obesity, and socioeconomic status.

[d]Neonates were defined as being LGA if their birthweight was greater than the 90th percentile and SGA if their birthweight was less than the 10th percentile based on national population references for age and sex (25).

CI, 95% confidence interval; LGA, large-for-gestational-age; OR, odds ratio; SGA, small-for-gestational-age.

Taylor *et al.* showed that a first trimester TSH level below 0.20 mIU/L was not associated with an increased risk of miscarriage in levothyroxine-treated women (14). They also found no association between TSH level measured in the first or second/third trimester, either below 0.30 mIU/L or greater than 10.00 mIU/L, and adverse obstetrical outcomes. Their results should, however, be interpreted with caution given the small number of participants in their groups. Our large study found that a TSH measurement <0.10 mIU/L at any time during pregnancy was associated with a significantly increased odds of preterm delivery, differing from the results of the other study (14). This may be due to our larger sample size, which provided adequate power to demonstrate this difference.

The current study's findings suggest that greater attention to clinical factors associated with TSH suppression may be required when adjusting levothyroxine dosage during pregnancy. Yassa *et al.* identified three factors that should potentially trigger a more conservative approach in the initial levothyroxine increase to prevent overtreatment (13). They found that athyreotic patients, females with a preconception TSH below 1.50 mIU/L, and those treated with a levothyroxine dose of at least 100 mcg/day before conception were at greater risk of TSH suppression <0.50 mIU/L during pregnancy following an initial levothyroxine dose increase. We conducted a *post hoc* analysis to further explore factors associated with TSH suppression <0.10 mIU/L during pregnancy in our population and this showed similar results. Our findings reinforced those of Yassa *et al.* and underscore the need for clinical judgment to guide the ATA's strong recommendation to increase levothyroxine dosage by 25–30% in all pregnant women. Indeed, a subgroup of pregnant women with preconception TSH <1.50 mIU/L or levothyroxine dose greater than 100 mcg/day may benefit from a more conservative approach to levothyroxine increments during pregnancy.

While the use of population-level administrative data provided a large sample size, the limitation of this approach is little detailed clinical information on the specific indications for TSH testing. Therefore, it is unknown whether the lack of TSH testing in some pregnancies was the result of some women not seeking medical care, the care provider not requesting a TSH, or the pregnant women not completing tests recommended by their care providers. Although we used a well-validated database to identify levothyroxine prescriptions, adjustments made in levothyroxine without issuing and filling a new prescription at the pharmacy would not have been taken into account in this study. This is important as many women planning a pregnancy are often instructed by their health care teams to take two extra tablets a week of their usual daily levothyroxine dosage once pregnancy is confirmed (4). Also, medication adherence could not be assessed in this study. It is possible that in addition to the confounders that were adjusted for, there may be other potential confounders that were not taken into account in our adjusted analysis. Finally, we are unable to assess early pregnancy loss in this study because our data sources only have information on pregnancies that completed at least 20 gestational weeks. Since other observational studies have found that undertreatment of hypothyroidism during pregnancy was associated with early pregnancy loss, clinicians also need to be careful to avoid undertreatment of hypothyroidism in pregnancy (10,23).

Our study has notable strengths, including the use of large population-based data sets to identify pregnant women on thyroid replacement before pregnancy. Indeed, unlike studies performed in a research setting, our study reflects practice patterns of management of thyroid disease in pregnancy in routine clinical practice from various practitioners. Moreover, the use of a large cohort allowed for the adjustment of multiple potential confounders. Finally, registering our protocol and analysis plan before data analysis is another important strength of this study, since it provides evidence that the reporting of data was complete and consistent with the initial analysis plans and not influenced by the study findings.

In conclusion, although most women on thyroid replacement before conception had TSH measured at some point during pregnancy, it is concerning that a sizeable proportion of these women (almost 20%) did not have a TSH measurement performed in pregnancy. Furthermore, this study found that levothyroxine overtreatment in pregnancy was associated with preterm delivery. Thus, until there are further dedicated studies on the management of preexisting hypothyroidism in pregnancy, clinicians should consider exercising caution to avoid overtreatment with levothyroxine in pregnancy.

Acknowledgments

The authors thank the Alberta Perinatal Health Program, including Susan Crawford, epidemiologist, who provided statistical support. They are also grateful to Jack M.S. Yeung, senior analyst, Alberta Health Services, for his work on data linkages for this study and to Patricia Johnson of Alberta Precision Laboratories for assistance with data collection.

Authors' Contributions

L.E.D., P.L., and J.M.Y. conceived and designed the study. L.E.D. curated the data (with input from A.C., K.A.N., and A.M.). L.E.D. was the project administrator and supervisor. P.L. wrote the first draft of the article. All the authors contributed to the critical review of the article. All the authors gave final approval of the version to be published. L.E.D. is the guarantor of this work.

Author Disclosure Statement

No competing financial interests exist for any of the authors.

Funding Information

This study was funded by the Alberta Children's Hospital Research Institute Seed Grant Fund (Grant No. 1002410). The funder had no role in study design or in the collection, analysis, or interpretation of the data, writing the article, or in the decision to submit the article for publication.

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Figure S1

References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC 2000 The Colorado thyroid disease prevalence study. Arch Intern Med **160:**526–534.
2. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ 2000 Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen **7:**127–130.
3. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG 2005 Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol **105:** 239–245.
4. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S 2017 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid **27:**315–389.
5. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR 2004 Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med **351:**241–249.
6. Abalovich M, Alcaraz G, Kleiman-Rubinsztein J, Pavlove MM, Cornelio C, Levalle O, Gutierrez S 2010 The relationship of preconception thyrotropin levels to requirements for increasing the levothyroxine dose during pregnancy in women with primary hypothyroidism. Thyroid **20:**1175–1178.
7. Loh JA, Wartofsky L, Jonklaas J, Burman KD 2009 The magnitude of increased levothyroxine requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism. Thyroid **19:**269–275.
8. Verga U, Bergamaschi S, Cortelazzi D, Ronzoni S, Marconi AM, Beck-Peccoz P 2009 Adjustment of L-T4 substitutive therapy in pregnant women with subclinical, overt or post-ablative hypothyroidism. Clin Endocrinol (Oxf) **70:**798–802.
9. Mandel SJ, Larsen PR, Seely EW, Brent GA 1990 Increased need for thyroxine during pregnancy in women with primary hypothyroidism. N Engl J Med **323:**91–96.
10. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O 2002 Overt and subclinical hypothyroidism complicating pregnancy. Thyroid **12:**63–68.
11. Kaplan MM 1992 Monitoring thyroxine treatment during pregnancy. Thyroid **2:**147–152.
12. Vadiveloo T, Mires GJ, Donnan PT, Leese GP 2013 Thyroid testing in pregnant women with thyroid dysfunction in Tayside, Scotland: the thyroid epidemiology, audit and research study (TEARS). Clin Endocrinol (Oxf) **78:** 466–471.
13. Yassa L, Marqusee E, Fawcett R, Alexander EK 2010 Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J Clin Endocrinol Metab **95:**3234–3241.
14. Taylor PN, Minassian C, Rehman A, Iqbal A, Draman MS, Hamilton W, Dunlop D, Robinson A, Vaidya B, Lazarus JH, Thomas S, Dayan CM, Okosieme OE 2014 TSH levels and risk of miscarriage in women on long-term levothyroxine: a community-based study. J Clin Endocrinol Metab **99:**3895–3902.
15. McClain MR, Lambert-Messerlian G, Haddow JE, Palomaki GE, Canick JA, Cleary-Goldman J, Malone FD, Porter TF, Nyberg DA, Bernstein P, D'Alton ME, FaSTER Research Consortium 2008 Sequential first- and second-trimester TSH, free thyroxine, and thyroid antibody measurements in women with known hypothyroidism: a FaSTER trial study. Am J Obstet Gynecol **199:**129.e121–e126.
16. Hallengren B, Lantz M, Andreasson B, Grennert L 2009 Pregnant women on thyroxine substitution are often dysregulated in early pregnancy. Thyroid **19:**391–394.
17. Granfors M, Akerud H, Berglund A, Skogö J, Sundström-Poromaa I, Wikström A-K 2013 Thyroid testing and management of hypothyroidism during pregnancy: a population-based study. J Clin Endocrinol Metab **98:**2687–2692.
18. Ashoor G, Rotas M, Maiz N, Kametas NA, Nicolaides KH 2010 Maternal thyroid function at 11–13 weeks of gestation in women with hypothyroidism treated by thyroxine. Fetal Diagn Ther **28:**22–27.
19. Wood SL, Tang S, Crawford S 2017 Cesarean delivery in the second stage of labor and the risk of subsequent premature birth. Am J Obstet Gynecol **217:**63.e1–63.e10.
20. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W, American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum 2011 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid **21:** 1081–1125.
21. Schneuer FJ, Nassar N, Tasevski V, Morris JM, Roberts CL 2012 Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes. J Clin Endocrinol Metab **97:**3115–3122.
22. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML,Hermos RJ, Waisbren SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med **341:**549–555.
23. Maraka S, Singh Ospina NM, O'Keeffe DT, Rodriguez-Gutierrez R, De Ycaza AEE, Wi C-I, Juhn YJ, Coddington CC 3rd, Montori VM 2017 Effects of increasing levothyroxine on pregnancy outcomes in women with uncontrolled hypothyroidism. Clin Endocrinol (Oxf) **86:**150–155.
24. Pampalon R, Hamel D, Gamache P, Raymond G 2009 A deprivation index for health planning in Canada. Chronic Dis Can **29:**178–191.
25. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, Blondel B, Bréart G, Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System 2001 A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics **108:**E35.

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