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ORIGINAL ARTICLE

Use of levothyroxine among pregnant women with subclinical hypothyroidism in the United Kingdom: A population-based assessment

Ya-Hui Yu[1,2] | Kristian B. Filion[2,3] | Pauline Reynier[2] | Robert W. Platt[2,4] | Oriana H. Y. Yu[2,5] | Sonia M. Grandi[1,2]

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

[2]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada

[3]Departments of Medicine and of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

[4]Departments of Pediatrics and of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

[5]Division of Endocrinology, Jewish General Hospital, Montreal, Quebec, Canada

Correspondence:
Sonia M. Grandi, Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 5750 Cote-des-Neiges, Montreal, Quebec H3T 1E2, Canada.
Email: sonia.grandi@mail.mcgill.ca

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Abstract

Our study aimed to describe levothyroxine prescription patterns and trends over time among pregnant women with subclinical hypothyroidism (SCH) in the United Kingdom.

We used data from the Clinical Practice Research Datalink linked to its Pregnancy Register and the Hospital Episode Statistics database from 1998 to 2017. The study population included women with a diagnosis of SCH or an abnormal thyroid-simulated hormone (TSH) level one year prior to or during pregnancy. We compared characteristics between women who received a prescription for levothyroxine during pregnancy and those who did not. We further described the timing, dose, duration, and temporal trends of levothyroxine prescriptions.

Our cohort included 6,757 pregnancies from 6,287 women with SCH, of whom 10% received levothyroxine during pregnancy. Among women who received levothyroxine, most received their first prescription during the first trimester (median gestational age: 7 weeks; interquartile range [IQR]: 0, 16) with a median daily dosage of 50 mcg (IQR: 50, 73). Levothyroxine prescription varied over time, decreasing from 23% of pregnant women in 1998 to 7.5% in 2003, remaining stable until 2014, and increasing to 12.5% in 2016. Smoking, diabetes, polycystic ovary syndrome, infertility, timing of SCH diagnosis, age, TSH level at diagnosis, and general practice regions were associated with prescription.

Few women with SCH received levothyroxine during pregnancy, and treatment varied by patient characteristics and geographical regions. These results highlight the need to increase awareness among healthcare providers and will guide future studies that explore barriers to initiating levothyroxine treatment for women with SCH during pregnancy.

KEYWORDS
drug utilization, levothyroxine, population-based cohort, pregnancy, subclinical hypothyroidism

Abbreviations: ATA, American Thyroid Association; CPRD, Clinical Practice Research Datalink; HES APC, Hospital Episode Statistics Admitted Patient Care; ICD-10, International Classification of Diseases; IQR, interquartile range; ONS, Office for National Statistics; SCH, subclinical hypothyroidism; TPOab, thyroid peroxidase antibodies; TSH, thyroid-simulated hormone.

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1 | INTRODUCTION

Subclinical hypothyroidism (SCH) commonly occurs during pregnancy, resulting from the increased metabolic demands that occur throughout pregnancy. It affects 2%–2.5% of pregnancies and is defined as having thyroid-stimulating hormone (TSH) levels above the trimester-specific reference with a normal thyroxine level.[1] Although current literature is inconsistent, some studies suggest that SCH is associated with an increased risk of adverse pregnancy outcomes (e.g., pregnancy loss).[2,3]

Although the benefits of treating overt hypothyroidism during pregnancy are well-established,[4] current evidence for treating SCH during pregnancy is inconclusive.[5–7] Due to potentially adverse consequences of SCH on mothers and infants, guidelines from the European Thyroid Association[1] and Endocrinology Society[8] recommend the use of levothyroxine for all women diagnosed with SCH during pregnancy. In contrast, the American Thyroid Association (ATA)[4,9] recommends treatment of SCH (TSH level >2.5 and <10 mU/L in 2011 guidelines; TSH level above the pregnancy-specific reference range in 2017 guidelines) in the presence of thyroid peroxidase antibodies (TPOab). Despite these recommendations, little is known about levothyroxine use for SCH during pregnancy in real-world settings. Previous studies reported the prevalence of levothyroxine prescribed among women with SCH during pregnancy, which ranged from 14% to 22% and varied with patient characteristics and clinical specialties of the prescriber.[10–13] However, studies of contemporary trends are lacking, and few reported treatment patterns of levothyroxine (e.g., timing, dose, duration). Furthermore, most of the previous studies were single-center studies,[10,11] with only one population-based study among privately insured patients in the United States (US).[13]

Our study aimed to examine the use of levothyroxine among women with SCH during pregnancy using data from a population-based cohort in the United Kingdom (UK). Our primary objective was to describe demographic, medical, and obstetric history for women with SCH prescribed levothyroxine during pregnancy, prescription patterns for levothyroxine, and prescription trends for levothyroxine over time.

2 | MATERIALS AND METHODS

2.1 | Data source

Our study cohort was constructed using the Clinical Practice Research Datalink (CPRD) Gold,[14] a population-based clinical database from >700 general practitioner practices in the UK. The CPRD includes information on demographics, medical diagnoses, prescriptions, lifestyle variables (e.g., body mass index [BMI]), laboratory test results, and clinical measures. Medical diagnoses and prescriptions are classified using Read Codes and the British National Formulary, respectively. Information on pregnancy was obtained from the CPRD Pregnancy Register.[15] We linked CPRD to the Hospital Episode Statistics Admitted Patient Care (HES APC) database and the Office for National Statistics (ONS) database for information on hospitalizations and deaths, respectively. HES contains in-hospital diagnoses recorded using the 10th version of the International Classification of Diseases (ICD-10) and procedures recorded using the 4th version of the Classification of Surgical Operations and Procedures (OPCS-4) codes, which were used to supplement diagnoses in the CPRD used to identify comorbidities, exclusion criteria, and censoring events. ONS uses ICD-9 (prior to 2001) and ICD-10 codes to record diagnoses. We linked CPRD to the Index of Multiple Deprivation[16] to obtain neighborhood deprivation scores to approximate socioeconomic status. Linked data are available for approximately 76% of English practices (58% of practices overall) starting on April 1, 1997. The data quality in CPRD and its linkage with other data has been previously validated.[17-19] The study cohort was restricted to patients who were linkable to HES because women with SCH are more likely to be followed by obstetricians and to deliver in a hospital.

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number: 19_022A3) and the Research Ethics Board of the Jewish General Hospital in Montreal, Canada. The study protocol was made available to journal reviewers.

2.2 | Study population

We included pregnancies of women, aged 15 to 45 years, with a recorded SCH diagnosis (identified by Read codes in CPRD and by ICD-10 code E.02 in HES) or an abnormal TSH value as defined below in the year prior to or during pregnancy. Inclusion was restricted to pregnancies starting between April 1, 1998 to March 31, 2017. This would ensure enough time to observe the entire pregnancy before the end of the study period (March 31, 2018). We extended the observation time to the year prior to pregnancy to better capture women with SCH not captured at prenatal visits. An abnormal TSH value was defined as >4 and <10 mU/L prior to pregnancy[20] and >2.5 and <10 mU/L during pregnancy. Cohort entry was defined by the date of SCH diagnosis or first abnormal TSH value or by the start of pregnancy, whichever occurred last.

A set of decision rules were used to reconcile overlapping pregnancies and remove duplicate pregnancy records. If overlapping pregnancies had the same outcomes, we kept the earlier record; for different outcomes, we prioritized records in the following order: stillbirth, livebirth, induced abortion, spontaneous abortion, and unknown outcomes.

Information in the CPRD Pregnancy Register was supplemented with data reported in the HES (Appendix). To increase validity, pregnancies with unknown outcomes and implausible gestational ages (<168 days for livebirth and stillbirth; <14 days for early pregnancy loss) were excluded.

We excluded pregnancies of women with <1 year of observation time in the CPRD at the start of pregnancy to ensure sufficient time to assess medical history. In addition, we excluded pregnancies of women with a history of treated hypothyroidism, defined as

ever having received a levothyroxine prescription and either a diagnostic code for hypothyroidism (including myxoedema, thyroiditis, Hashimoto's disease) or a TSH value ≥10 mU/L prior to cohort entry. We also excluded pregnancies of women with histories of thyroid cancer, hyperthyroidism (including Graves' disease, thyrotoxicosis, toxic goiter), and/or thyroidectomy to avoid including women using levothyroxine for other indications. Finally, pregnancies of women with a contraindication for levothyroxine[21] were excluded.

All pregnancies were followed from cohort entry until the end of the pregnancy or censoring due to the earliest of the following: the end of registration in the CPRD, diagnosis of thyroid disorders other than SCH, a TSH level ≥10 mU/L, or contraindication for levothyroxine. The time intervals used for cohort construction are illustrated in Figure S1.

2.3 | Levothyroxine use

Levothyroxine use was defined as having ≥1 prescription during pregnancy or a prescription prior to cohort entry that overlapped with the cohort entry date. The prescription duration was based on the number of recorded days or derived as the quantity of medication divided by the recommended dosage.

2.4 | Baseline characteristics

We assessed the following variables: practice-level factors (region in the UK, Index of Multiple Deprivation at the practice location), maternal demographics (age, race/ethnicity), lifestyle factors (BMI, smoking status, excessive alcohol use), characteristics of the current pregnancy (gravidity, parity, multiple gestation, year of pregnancy started), comorbidities (diabetes, hypertension, rheumatoid arthritis, polycystic ovary syndrome, infertility), and obstetric history (miscarriage, stillbirth, infant mortality, preterm birth, gestational diabetes, hypertensive disorder in pregnancy). Comorbidities were defined using Read codes in the CPRD and ICD-10 codes in HES or by a prescription of a disease-specific medication before the start of pregnancy. BMI and smoking were defined using the last recorded measurement in the 3 years prior to pregnancy. Race/ethnicity was classified using five categories: White (British, Irish, other white), South Asian (Bangladeshi, Indian, Pakistani, other Asian), Black (African, Caribbean, Black British); Mixed (White and Asian, White and African, White and Caribbean, other mixed), and other.[22]

2.5 | Statistical analysis

2.5.1 | Primary analyses

We compared the distributions of patient characteristics between women receiving and not receiving levothyroxine during pregnancy. Categorical variables were presented as counts and percentages; continuous variables were summarized as means and standard deviations. Absolute standardized differences >0.1 between two treatment groups were considered important.[23]

Patterns of levothyroxine prescription were described by the daily dose of the first prescription during pregnancy, dose adjustment during pregnancy, proportion of use by gestational age, and median duration of use during pregnancy. The duration of use was also reported by the proportion of patient follow-up time to account for different cohort entry times and lengths of pregnancy. We used the Kaplan–Meier approach to estimate the cumulative incidence of levothyroxine use during follow-up. We conducted analyses overall and by the timing of SCH diagnosis.

Temporal trends in the prescription of levothyroxine during pregnancy were described as the proportion of pregnancies exposed by calendar year, defined by the pregnancy start date and grouped by fiscal year (April to March). ATA Guidelines[4] suggest that TSH levels at SCH diagnosis are the main determinant for prescribing levothyroxine. Therefore, we assessed whether the distribution of TSH levels at diagnosis varied over time between treatment groups; we stratified these analyses by TSH cutoffs used to diagnose SCH, which differ prepregnancy and during pregnancy.

We used multivariable logistic regression to determine characteristics independently associated with the prescription of levothyroxine for SCH during pregnancy, including all patient-level and practice-level characteristics. We included all of the variables of interest in the model without applying any additional variable selection since our goal was not to develop a formal prediction model. Several variables had missing values in our analytic cohort: BMI (30%), multiple pregnancies (21%), smoking status (17%), race/ethnicity (1%), and TSH level at diagnosis (0.1%). We used the multiple imputations by the chained equations method[24] to impute missing values and generated 10 complete datasets. Rubin's rule[25] was used to combine coefficients across the imputed datasets. Our imputation models included the variables listed in the baseline characteristics section with less than 40% missing values, TSH level at diagnosis, gestational age, and levothyroxine treatment. We assumed the missing data mechanism was missing at random.

2.5.2 | Sensitivity analyses

The definition of SCH varied throughout our study period (1998–2017); therefore, we examined levothyroxine prescription rates in cohorts defined using various definitions of SCH to explore the potential impact of diagnoses on the rates of prescriptions for levothyroxine. For women without a SCH diagnostic code, we defined SCH using four different laboratory measurements: (1) A TSH value within the trimester-specific abnormal range defined as prepregnancy: >4 and <10 mU/L; first-trimester: >2.5 and <10 mU/L; second and third trimester: >3 and <10 mU/L[9] (2) An abnormal TSH value, defined >4 and <10 mU/L prepregnancy and >2.5 and <10 mU/L during pregnancy, with a normal free thyroxine (FT4) value (≥9 pmol/ dL)[26] (3) An abnormal TSH value defined by the trimester-specific TSH threshold and a normal FT4 value (4) A TSH

value >4 mU/L and a normal FT4 value. About half of the women in our cohort had a prescribed FT4 test within a week after an abnormal TSH value. Therefore, we adopted two approaches: one was to constrain to those with prescribed FT4 tests, and the other was to impute FT4 values for those without a prescribed test.

All statistical analyses were performed in SAS 9.4 (SAS Institute) and R 3.6.

3 | RESULTS

3.1 | Patient characteristics

Our study cohort included 6,757 pregnancies from 6,287 women with SCH (Figure 1), and the median follow-up time was 221 days (IQR: 84, 272). Characteristics of patients with SCH diagnosed prepregnancy were similar to those diagnosed during pregnancy, except for obesity and history of infertility (Table S1). Among women diagnosed during pregnancy, the median gestational week of SCH diagnosis was 8 weeks (IQR: 4, 18). A total of 644 (10%) women with SCH were prescribed levothyroxine during pregnancy.

The characteristics of pregnant women with SCH were described by treatment status (Table 1). Compared to women who were not prescribed levothyroxine, women prescribed levothyroxine were more likely older, self-reported as white, overweight or obese, and nonsmokers. They were also more likely to be registered with general practices in less deprived areas, diagnosed with SCH prior to pregnancy or during the second trimester, have higher TSH values at diagnosis, and higher gravidity and parity. They also had a higher prevalence of comorbidities, including histories of diabetes, polycystic ovary syndrome, or infertility; obstetrical histories were similar between the two groups. The distribution of geographic regions of general practitioner practices differed among treated and untreated women.

3.2 | Characteristics of levothyroxine prescription

Among women prescribed levothyroxine, most received a prescription within 60 days after cohort entry and 50% were prescribed within 8 days (IQR: 0, 39) of cohort entry (Figure S2). The median gestational age at first prescription was 7 weeks (IQR: 0, 16), and the median daily dose at first prescription was 50 mcg (IQR: 50, 72.6) (Figure S3). These women received a median number of four prescriptions (IQR: 2, 6), and 17% of patients only received one during pregnancy. Approximately 46% of women had a dose adjustment during pregnancy, with a median of 3 (IQR: 2, 5) adjustments during follow-up. The majority of dose adjustments occurred during the second and third trimesters (1st trimester: 23%, 2nd trimester: 40%, 3rd trimester: 37%), with a median dose adjustment of 50 mcg (25, 75). Half of the women prescribed levothyroxine received prescriptions for ≥80% of their follow-up (Figure S4), and the median overall duration of use was 144 days (IQR: 72, 216). Among women prescribed levothyroxine during pregnancy, the proportion of use varied by gestational age. The proportion of use was lower in the first trimester and rapidly increased during the second trimester; about 85% of these women were used throughout the third trimester (Figure S5). Compared to women diagnosed with SCH prior to pregnancy, women diagnosed during pregnancy had a longer time to first levothyroxine prescription (median days [IQR]: 19 [7, 47] vs. 0 [0, 19]) (Figure S2). The daily dose during pregnancy was higher among those diagnosed during the second or third trimesters compared to those diagnosed prior to pregnancy or during the first trimester (median [IQR]: 75 [50,100] vs. 50 [50,100] mcg) (Figure S3). Women diagnosed during pregnancy also had fewer total days of use (median [IQR]: 117 [57, 171] vs. 191 [82, 254]) and a smaller proportion of their follow-up time using levothyroxine (median [IQR]: 71 [54, 88]) vs. 87 [67, 98]) (Figure S4).

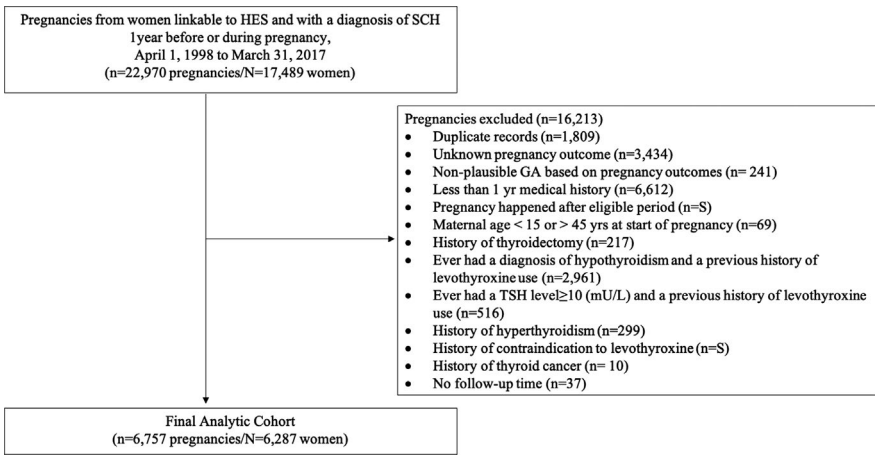

FIGURE 1 Flowchart of analytic cohort selection of pregnant women with subclinical hypothyroidism in the United Kingdom, Clinical Practice Research Datalink and Hospital Episode Statistics databases, 1998–2017. S: based on data regulations for CPRD, for cell counts <5, more than 1 cell needs to be suppressed to avoid being back calculated

TABLE 1 Characteristics of pregnant women with subclinical hypothyroidism in the United Kingdom between 1998 and 2017, by levothyroxine treatment status[a]

	Total pregnancy (n = 6,757)	Not prescribed levothyroxine (n = 6,093)	Prescribed levothyroxine (n = 664)	Standardized difference
Age, (year), n (%)				0.407
<20	369 (5.5)	359 (5.9)	10 (1.5)	
20–29	2,113 (31.3)	1,983 (32.5)	130 (19.6)	
>29	4,275 (63.3)	3,751 (61.6)	524 (78.9)	
Timing of SCH diagnosis, n (%)				0.309
Prepregnancy	2,860 (42.3)	2,507 (41.1)	353 (53.2)	
First trimester	2,548 (37.7)	2,357 (38.7)	191 (28.8)	
Second trimester	851 (12.6)	755 (12.4)	96 (14.5)	
Third trimester	498 (7.4)	474 (7.8)	24 (3.6)	
TSH level at diagnosis, mean (SD)				
SCH diagnosed prepregnancy	5.3 (1.3)	5.2 (1.2)	6.0 (1.5)	0.604
SCH diagnosed during pregnancy	3.6 (1.2)	3.5 (1.1)	4.7 (1.8)	0.814
Race/ethnicity, n (%)				0.102
White	5,615 (83.1)	5,061 (83.1)	554 (83.4)	
Mixed	96 (1.4)	83 (1.4)	13 (2.0)	
South Asian	723 (10.7)	650 (10.7)	73 (11.0)	
Black	141 (2.1)	134 (2.2)	7 (1.1)	
Others	182 (2.7)	165 (2.7)	17 (2.6)	
Year pregnancy started, n (%)				0.115
1998–2003	761 (11.3)	680 (11.2)	81 (12.2)	
2004–2009	2,676 (39.6)	2,442 (40.1)	234 (35.2)	
2010–2014	2,711 (40.1)	2,436 (40.0)	275 (41.4)	
2015–2017	609 (9.0)	535 (8.8)	74 (11.1)	
Index of multiple deprivation (practice-level), n (%)				0.299
1 (least deprived)	1,209 (17.9)	1,047 (17.2)	162 (24.4)	
2	1,216 (18.0)	1,091 (17.9)	125 (18.8)	
3	1,215 (18.0)	1,082 (17.8)	133 (20.0)	
4	1,414 (20.9)	1,271 (20.9)	143 (21.5)	
5	1,703 (25.2)	1,602 (26.3)	101 (15.2)	
Region in the United Kingdom (practice-level), n (%)				0.320
North East	191 (2.8)	164 (2.7)	27 (4.1)	
North West	1,050 (15.5)	995 (16.3)	55 (8.3)	
Yorkshire & The Humber	172 (2.5)	151 (2.5)	21 (3.2)	
East Midlands	175 (2.6)	162 (2.7)	13 (2.0)	
West Midlands	843 (12.5)	764 (12.5)	79 (11.9)	
East of England	641 (9.5)	550 (9.0)	91 (13.7)	
South West	844 (12.5)	773 (12.7)	71 (10.7)	
South Central	956 (14.1)	856 (14.0)	100 (15.1)	
London	1,100 (16.3)	996 (16.3)	104 (15.7)	
South East Coast	785 (11.6)	682 (11.2)	103 (15.5)	
Body mass index (kg/m^2)[b], n (%)				0.096
Underweight (<18.5)	168 (2.5)	153 (2.5)	15 (2.3)	
Normal weight (18.5–24.9)	2,624 (38.8)	2,392 (39.3)	232 (34.9)	

(Continues)

TABLE 1 (Continued)

	Total pregnancy (n = 6,757)	Not prescribed levothyroxine (n = 6,093)	Prescribed levothyroxine (n = 664)	Standardized difference
Overweight (25–29.9)	2,478 (36.7)	2,213 (36.3)	265 (39.9)	
Obesity (≥30)	1,487 (22.0)	1,335 (21.9)	152 (22.9)	
Smoking status[b], n (%)				0.234
Non-smoker	4,338 (64.2)	3,871 (63.5)	467 (70.3)	
Ex-smoker	1,056 (15.6)	941 (15.4)	115 (17.3)	
Current smoker	1,363 (20.2)	1,281 (21.0)	82 (12.3)	
Excessive alcohol use[c], n (%)	263 (3.9)	247 (4.1)	16 (2.4)	0.093
Comorbidities[c]				
Diabetes mellitus, n (%)	377 (5.6)	314 (5.2)	63 (9.5)	0.167
Hypertension, n (%)	333 (4.9)	299 (4.9)	34 (5.1)	0.010
Rheumatoid arthritis, n (%)	129 (1.9)	112 (1.8)	17 (2.6)	0.049
Polycystic ovary syndrome, n (%)	476 (7.0)	405 (6.6)	71 (10.7)	0.144
Infertility, n (%)	1,462 (21.6)	1,274 (20.9)	188 (28.3)	0.173
Gravidity, n (%)				0.115
0	2,540 (37.6)	2,314 (38.0)	226 (34.0)	
1–2	3,190 (47.2)	2,846 (46.7)	344 (51.8)	
3–4	815 (12.1)	736 (12.1)	79 (11.9)	
≥5	212 (3.1)	197 (3.2)	15 (2.3)	
Parity, n (%)				0.102
0	3,408 (50.4)	3,092 (50.7)	316 (47.6)	
1–2	2,957 (43.8)	2,643 (43.4)	314 (47.3)	
3–4	340 (5.0)	308 (5.1)	32 (4.8)	
≥5	52 (0.8)	S	S	
Multiple gestations, n (%)	59 (0.9)	S	S	0.015
Obstetrics history[c]				
Miscarriage, n (%)	1,437 (21.3)	1,276 (20.9)	161 (24.2)	0.079
Stillbirth, n (%)	57 (0.8)	51 (0.8)	6 (0.9)	0.007
Infant mortality, n (%)	13 (0.2)	S	S	0.025
Preterm birth, n (%)	279 (4.1)	256 (4.2)	23 (3.5)	0.038
Gestational diabetes, n (%)	93 (1.4)	85 (1.4)	8 (1.2)	0.017
Hypertensive disorder in pregnancy, n (%)	269 (4.0)	239 (3.9)	30 (4.5)	0.030

Abbreviations: S, based on data regulations for CPRD, for cell counts <5, more than 1 cell needs to be suppressed to avoid being back calculated; SCH, subclinical hypothyroidism; SD, standard deviation; TSH, thyroid-stimulating hormone.

[a]There were variables with missing values: BMI (30%), multiple pregnancies (21%), smoking status (17%), race/ethnicity (1%), TSH level at diagnosis (0.1%). For these variables, the numbers represent average values across 10 imputed datasets for continuous variables; for categorical variables, the mode of the proportions across 10 imputed datasets are presented.

[b]Assessed using the last recorded measurement within 3 years prior to the pregnancy.

[c]Assessed in any time prior to the pregnancy.

3.3 | Temporal trends of levothyroxine prescription during pregnancy

The proportion of women prescribed levothyroxine during pregnancy varied across calendar years (Figure 2), decreasing from 23% in 1998 to 7.5% in 2003, with the prevalence of use remaining stable until 2014 before increasing to 12.5% in 2016. The magnitude of the difference in TSH at diagnosis between patients prescribed and not prescribed levothyroxine varied over calendar time. The difference in TSH level between two groups was much smaller in more recent years (2014–2017), since TSH levels of women using levothyroxine decreased over time. This trend was more pronounced in women with SCH diagnosed during pregnancy (Figure 3).

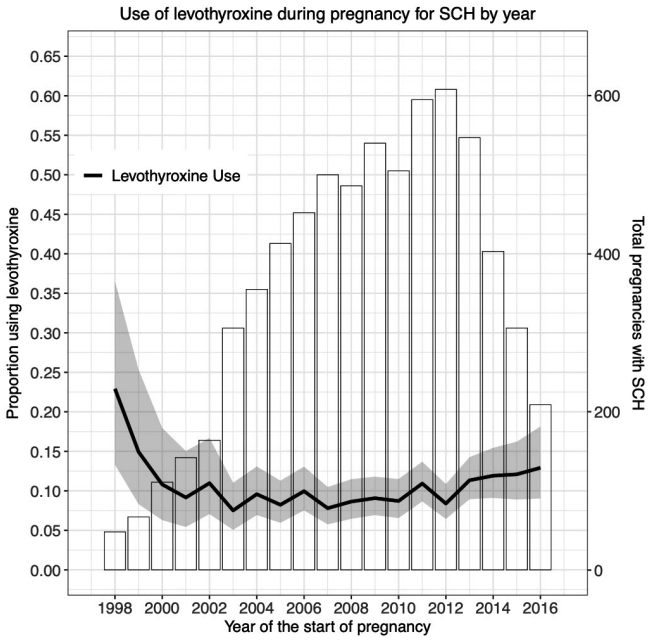

FIGURE 2 Levothyroxine prescription by year of pregnancy in women with subclinical hypothyroidism in the United Kingdom, from 1998 to 2017. Each time interval starts from April 1 to March 31 of the next year SCH = subclinical hypothyroidism

3.4 | Characteristics associated with levothyroxine prescription

Several patient and practice-level characteristics were independently associated with levothyroxine prescription (Figure S6). These included smoking, histories of diabetes, polycystic ovary syndrome, or infertility, year of pregnancy, timing of SCH diagnosis, age, TSH level at diagnosis, deprivation index, and geographic region of the general practice. We further examined the characteristics related to remaining untreated among a subcohort of women who indeed received a SCH diagnostic code or had a relatively high TSH (>4 and <10 mU/L) within the abnormal range (Figure S7). Those who remained unprescribed levothyroxine in this subcohort were more likely to be current smoker, younger than 20, without diabetes, preganancy started prior to 2009, diagnosed with SCH prior to pregnancy, and have low TSH values at diagnosis. They were also more likely to be registered with general practices in more deprived areas.

3.5 | Sensitivity analyses

Using the various SCH definitions, the levothyroxine prescription rates ranged from 10% to 14% (Table S2) with the highest rate among those with SCH defined by diagnostic codes or by a TSH >4 mU/L with a normal FT4 level. When comparing our two approaches to deal with missing FT4 values, the prescription rates were slightly higher in the cohort constrained to those with prescribed FT4 tests than in the cohort with imputed FT4 values (Table S2). However, the characteristics of women with a FT4 test prescribed within one week of an abnormal TSH level were distinct from those without a prescribed test (Table S3). Thyroxine levels were more likely to be tested among women with SCH diagnosed prepregnancy or among those with higher TSH levels and by general practices in specific geographic regions.

4 | DISCUSSION

In this population-based cohort, we found that only 10% of women with SCH during pregnancy were prescribed levothyroxine in the UK between 1998 and 2017. The prescription rates remained low with the highest rate of 14% when applying different SCH definitions. Compared with women not prescribed levothyroxine during pregnancy, women prescribed levothyroxine were more likely to be older, non-smokers, have recorded pregnancies at more recent years (2015–2017), have higher TSH levels at diagnosis, and histories of diabetes, polycystic ovary syndrome, or infertility. Prescriptions for levothyroxine also varied with geographic region and socioeconomic status. Although prescriptions for levothyroxine increased approximately 1.5-fold during the study period, prescription rates remained low (12.5%) in 2016–2017. In more recent years, TSH levels at diagnosis did not differ by treatment status. Among levothyroxine-treated women, most were prescribed within 60 days after cohort entry and continued throughout pregnancy. Our results suggest that over a 20-year period, many women with SCH remained untreated during pregnancy. The choice of whether to prescribe varied based on pre-existing conditions and practice, which presents an opportunity to improve prescribing practices of levothyroxine for women with SCH.

The use of levothyroxine for women with SCH during pregnancy has been examined.[11–13] In a study[11] conducted in a US medical center of 366 women with SCH from 2011 to 2013, 22% received levothyroxine during pregnancy. Another US population-based cohort[12,13] found only 16% of women (n = 5,405) were treated for SCH during pregnancy from 2010 to 2014. Both studies observed increasing trends in levothyroxine use over time. Compared to these studies, our study showed a lower proportion of women prescribed (ranged from 10 to 14%) levothyroxine. The discrepancy may stem from different cohort compositions, since these studies excluded patients using levothyroxine prior to baseline and did not exclude patients with hypothyroidism.

Despite differences in study populations, characteristics of levothyroxine prescribing patterns in other studies are similar to ours regarding median time to first prescription (11 days [IQR: 4–15]),[12] median gestational age at first prescription (9.1 weeks [IQR: 7.7–11.5]).[11] They also have similar treatment duration (average of 88% of follow-up times),[12] and daily dosage at first prescription (50 mcg [IQR: 25–62.5]).[12]

Similar to previous studies, our study identified several characteristics were associated with levothyroxine prescription during pregnancy including older age, higher TSH levels at diagnosis, and

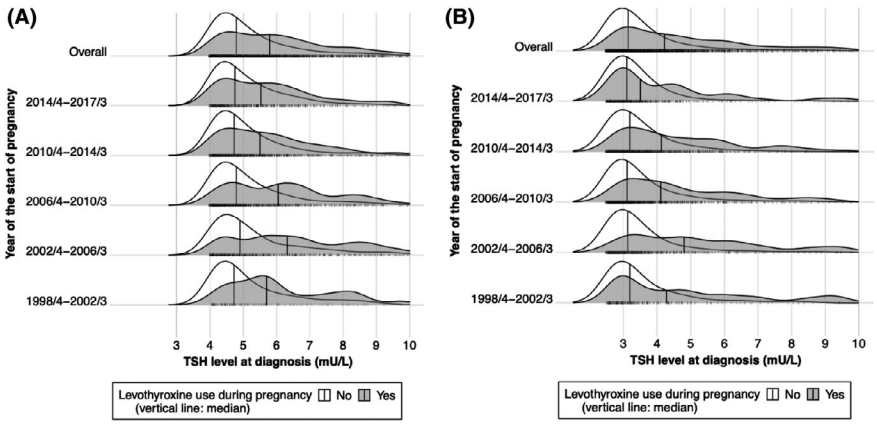

FIGURE 3 Thyroid-stimulating hormone level at diagnosis by levothyroxine use and year of pregnancy in women with subclinical hypothyroidism in the United Kingdom, from 1998 to 2017. (A) Among women with subclinical hypothyroidism diagnosed prepregnancy; (B) Among women with subclinical hypothyroidism diagnosed during pregnancy. Distributions of thyroid-stimulating hormone level were presented by density plots with vertical lines indicating median of thyroid-stimulating hormone level of each distribution. Rug plots under the distributions represent the counts of pregnancies at the thyroid-stimulating hormone level. TSH = thyroid-stimulating hormone

thyroid disorder history.[13] In contrast to other studies,[11,13] we found that diabetes history was also associated with levothyroxine prescription. It is plausible that clinicians were encouraged to treat SCH during pregnancy to improve the management of diabetes,[20,27] since hypothyroidism has been linked to insulin sensitivity[28,29] and metabolic abnormalities.[30]

There is currently no consensus regarding the clinical management of women with SCH during pregnancy. This equipoise is well-illustrated by the heterogeneity of recommendations among international treatment guidelines.[1,4,8,9] In addition, this equipoise is reflected by the heterogeneity of practice patterns observed across geographic regions in our study. This is consistent with a US utilization study that showed variations in prescribing patterns across different specialists,[13] as well as studies examining clinical perceptions of practices for SCH management in pregnancy.[31,32] This heterogeneity may be explained by emerging concerns[33] about the harms of overtreating, and uncertainties about the benefits of treating SCH with levothyroxine during pregnancy.[34-36] Future high-quality studies are warranted to examine the safety and effectiveness of levothyroxine for women with SCH on health outcomes of mothers and their offspring. In addition, future research is needed to better understand the clinician's perception and barriers to levothyroxine treatment among patients with SCH. This research may help improve the clinical consensus on the management of SCH during pregnancy.

Our study has several potential limitations. First, SCH diagnosis may not be recorded at each encounter with a general practitioner in the CPRD and point of care (secondary/specialist care) where patients received SCH diagnosis may also impact the timing of recording in the CPRD. Therefore, we added a 1-year grace period prior to pregnancy to identify SCH diagnoses among women who may not have a SCH diagnosis recorded during prenatal visits. To account for the potential difference with respect to patient characteristics of women diagnosed prepregnancy and during pregnancy, we described treatment patterns stratified by timing of SCH diagnosis. We did not consider including women with a SCH diagnosis beyond 1 year prior to pregnancy since we were interested in capturing the most recent episode of SCH prior to pregnancy. To further understand the impact of extending the grace period, we conducted a sensitivity analysis using a 3-year grace period prior to pregnancy to capture SCH diagnoses. We identified 2,802 additional women with SCH, however, only 6% of them were prescribed levothyroxine during pregnancy which was lower than the rate of our main analyses. Second, the prevalence of SCH diagnostic codes were very low in our cohort (0.8%) therefore, we leveraged laboratory measurements to identify women with SCH. This may introduce inaccurate SCH ascertainment which may potentially result in low observed levothyroxine prescription rates. TSH cutoff levels for SCH definitions evolved throughout the study period (1998–2017) and were recommended to be tailored based on ethnicity. For example, in 2011, ATA proposed the following upper limits of the trimester-specific reference ranges when no local reference available: first trimester: 2.5 mU/L; second and third: 3.0 mU/L,[8,9] whereas in 2014, the European Thyroid Association proposed 3.5 mU/L for the third trimester.[1] In 2017, ATA updated the upper limits at the first trimester as 4 mU/L.[4] Therefore, we conducted a series of sensitivity analyses adapting different TSH cutoff levels recommended in the American and European guidelines and found that the prescription rates were slightly higher than the rates in the main analyses but remained relatively low. Third, our cohort included women with SCH identified from CPRD GOLD and HES, which include women receiving care from general practitioners or in hospitals. Although specialists are encouraged to send patient reports to general practitioners, who are considered the gatekeepers to the UK healthcare systems, there is a possibility that women receiving care for SCH from other clinicians (e.g., midwives, obstetricians) may not be included in our study, which may potentially introduce selection bias. Fourth, thyroxine level was not used as part of our definition for SCH in the main analysis since only half of the women had reported values within a week of their TSH measurement. As these women were highly selected with distinct characteristics, applying

this criterion only to those with prescribed tests may result in selection bias. This may partly explain the different prescription rates between this subcohort versus overall population with imputed FT4 level in our sensitivity analyses. Lack of uniform testing was seen in a study[37] in which only one-third of women were prescribed a thyroxine test. To avoid including overt hypothyroidism, we excluded women with a history of treated hypothyroidism prior to cohort entry. Fifth, previous studies have shown benefits of treating women who present as TPOab positive.[38,39] However, we were not able to assess if TPOab is associated with levothyroxine prescription because only 3% of women had tests within two weeks of their TSH measurement. Similar to thyroxine tests, TPOab testing was not routinely performed in clinical practice during the study period. Sixth, there is the possibility for exposure misclassification since the CPRD does not capture drugs prescribed during hospitalization or by specialists. We expect the number of affected patients to be low since most outpatient prescriptions in the UK are from general practitioners. In addition, for those patients who were prescribed levothyroxine initially by specialists, their general practitioners would usually receive reports and recommendations for continued use from specialists. Based on our study, we found most exposed women (83%) received multiple prescriptions during pregnancy. Although we may not be able to capture the earliest prescription from specialists, we were able to capture subsequent prescriptions written by general practitioners. Upon further examination, women receiving only one prescription had a slightly longer time from cohort entry to treatment initiation compared to those who received multiple prescriptions (median 15 days [IQR: 2, 47] vs. 6 days [IOR: 0, 35]). This suggests that missing specialists' prescriptions likely had a modest impact on our study results. Finally, for women diagnosed with SCH and prescribed treatment before pregnancy, current clinical guidelines recommend that they self-administer a 25–30% dose increase once aware of the pregnancy.[4] This self-administered dosage increase is not reflected in our dataset and therefore, there is the possibility of an under-estimated dose of their first prescription during pregnancy.

5 | CONCLUSIONS

Our study found that a low proportion of women with SCH were prescribed levothyroxine during pregnancy and that prescriptions varied by patient characteristics and geographical region. These results provide insight on real-world utilization of levothyroxine among women with SCH during pregnancy and trends over a 20-year period in the UK. This work provides an opportunity to increase awareness among healthcare professionals regarding the use of levothyroxine for SCH during pregnancy and to guide future studies to explore barriers to initiating levothyroxine treatment among women with SCH during pregnancy.

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DISCLOSURES

RWP holds the Albert Boehringer I Chair in Pharmacoepidemiology and has received personal fees from Amgen, Analysis Group, Merck, and Pfizer, all outside of the submitted work.

AUTHOR CONTRIBUTIONS

YHY, SMG, and KBF conceived the study idea in consultation with all other co-authors. YHY conducted the analyses and PR provided critical input during the analytic stage of this study. YHY wrote the initial draft of the manuscript and all other authors reviewed the manuscript for intellectual content. All authors approved the submitted manuscript.

ETHICS APPROVAL

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number: 19_022A3) and the Research Ethics Board of the Jewish General Hospital in Montreal, Canada (reference number: 2019–1698; approved March 28, 2019).

DATA AVAILABILITY STATEMENT

Data used in this study were not available to share due to the data usage agreement with Clinical Practice Research Datalink.

ORCID

Kristian B. Filion https://orcid.org/0000-0001-6055-0088
Robert W. Platt https://orcid.org/0000-0002-5981-8443
Sonia M. Grandi https://orcid.org/0000-0002-8576-7854

REFERENCES

1. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3(2):76-94.
2. van den Boogaard E, Vissenberg R, Land JA, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update*. 2011;17(5):605-619.
3. Maraka S, Ospina NMS, O'Keeffe DT, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. *Thyroid*. 2016;26(4):580-590.
4. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):315-389.
5. Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism prepregnancy and during pregnancy. *Cochrane Database Syst Rev*. 2013;(5):CD007752 PMID: 23728666.
6. Velkeniers B, Van Meerhaeghe A, Poppe K, Unuane D, Tournaye H, Haentjens P. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted

reproduction technologies: systematic review and meta-analysis of RCTs. *Hum Reprod Update*. 2013;19(3):251-258.
7. Nazarpour S, Ramezani Tehrani F, Amiri M, Bidhendi Yarandi R, Azizi F. Levothyroxine treatment and pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2019;300(4):805-819.
8. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(8):2543-2565.
9. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21(10):1081-1125.
10. Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. *J Endocrinol Invest*. 2012;35(3):322-325.
11. Maraka S, Singh Ospina NM, O'Keeffe DT, et al. Effects of levothyroxine therapy on pregnancy outcomes in women with subclinical hypothyroidism. *Thyroid*. 2016;26(7):980-986.
12. Maraka S, Mwangi R, McCoy RG, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. *BMJ*. 2017;25:356.
13. Maraka S, Mwangi R, Yao X, et al. Variation in treatment practices for subclinical hypothyroidism in pregnancy: US national assessment. *J Clin Endocrinol Metab*. 2019;104(9):3893-3901.
14. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.
15. Minassian C, Williams R, Meeraus WH, Smeeth L, Campbell OMR, Thomas SL. Methods to generate and validate a pregnancy register in the UK Clinical Practice Research Datalink primary care database. *Pharmacoepidemiol Drug Saf*. 2019;28(7):923-933.
16. English indices of deprivation 2015 (access at 1/14/2021). GOV.UK. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015
17. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69(1):4-14.
18. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract J R Coll Gen Pract*. 2010;60(572):e128-e136.
19. Padmanabhan S, Carty L, Cameron E. Approach to record linkage of primary care data from clinical practice research datalink to other health-related patient data: overview and implications. *Eur J Epidemiol*. 2019;(34):91.
20. Pearce SHS, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J*. 2013;2(4):215-228.
21. Synthyroid Product Monograph (access at 9/21/2020). Available from: https://www.mylan.ca/-/media/mylanca/documents/english/product%20pdf/1.3.1-synthroid-pm.pdf
22. Mathur R, Bhaskaran K, Chaturvedi N, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health Oxf Engl*. 2014;36(4):684-692.
23. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107.
24. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(1):1-67.
25. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc*. 1996;91(434):473-489.
26. Thyroid function tests British Thyroid Foundation. Available from: https://www.btf-thyroid.org/thyroid-function-tests
27. Kalra S, Aggarwal S, Khandelwal D. Thyroid dysfunction and type 2 diabetes mellitus: screening strategies and implications for management. *Diabetes Ther*. 2019;10(6):2035-2044.
28. Maratou E, Hadjidakis DJ, Kollias A, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *Eur J Endocrinol*. 2009;160(5):785-790.
29. Stanická S, Vondra K, Pelikánová T, Vlcek P, Hill M, Zamrazil V. Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. *Clin Chem Lab Med*. 2005;43(7):715-720.
30. Yang L, Lv X, Yue F, Wei D, Liu W, Zhang T. Subclinical hypothyroidism and the risk of metabolic syndrome: a meta-analysis of observational studies. *Endocr Res*. 2016;41(2):158-165.
31. Vaidya B, Hubalewska-Dydejczyk A, Laurberg P, Negro R, Vermiglio F, Poppe K. Treatment and screening of hypothyroidism in pregnancy: results of a European survey. *Eur J Endocrinol*. 2012;166(1):49-54.
32. Toloza FJK, Singh Ospina NM, Rodriguez-Gutierrez R, et al. Practice variation in the care of subclinical hypothyroidism during pregnancy: a national survey of physicians in the United States. *J Endocr Soc*. 2019;3(10):1892-1906.
33. Velasco I, Taylor P. Identifying and treating subclinical thyroid dysfunction in pregnancy: emerging controversies. *Eur J Endocrinol*. 2018;178(1):D1-D12.
34. Wiles KS, Jarvis S, Nelson-Piercy C. Are we overtreating subclinical hypothyroidism in pregnancy? *BMJ*. 2015;351.
35. Derakhshan A, Peeters RP, Taylor PN, et al. Association of maternal thyroid function with birthweight: a systematic review and individual-participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2020;8(6):501-510.
36. Dhillon-Smith RK. Maternal thyroid function, levothyroxine, and birthweight—a balancing act. *Lancet Diabetes Endocrinol*. 2020;8(6):461-462.
37. Blatt AJ, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. *J Clin Endocrinol Metab*. 2012;97(3):777-784.
38. Ying H, Tang Y-P, Bao Y-R, et al. Maternal TSH level and TPOAb status in early pregnancy and their relationship to the risk of gestational diabetes mellitus. *Endocrine*. 2016;54(3):742-750.
39. Liu H, Shan Z, Li C, et al. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. *Thyroid*. 2014;24(11):1642-1649.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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