TSH Levels and Risk of Miscarriage in Women on Long-Term Levothyroxine: A Community-Based Study

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Context: Thyroid dysfunction is associated with adverse obstetric outcomes, but there is limited information on pregnancy outcomes in women established on levothyroxine.

Objective: The objective of the study was to determine the relationship between TSH levels and pregnancy outcomes in levothyroxine-treated women in a large community-based database.

Design: This was a historical cohort analysis.

Patients: Individuals with a first prescription of levothyroxine from 2001 through 2009 (n = 55 501) were identified from the UK General Practice Research Database (population 5 million). Of these, we identified 7978 women of child-bearing age (18–45 y) and 1013 pregnancies in which levothyroxine had been initiated at least 6 months before conception.

Main Outcome Measures: TSH, miscarriage/delivery status, and obstetric outcomes were measured.

Results: Forty-six percent of levothyroxine-treated women aged 18–45 years had a TSH level greater than 2.5mU/L (recommended upper level in the first trimester). Among pregnant women who had their TSH measured in the first trimester, 62.8% had a TSH level greater than 2.5 mU/L, with 7.4% greater than 10 mU/L. Women with TSH greater than 2.5 mU/L in the first trimester had an increased risk of miscarriage compared with women with TSH 0.2–2.5 mU/L after adjusting for age, year of pregnancy, diabetes, and social class ($P = .008$). The risk of miscarriage was increased in women with TSH 4.51–10 mU/L [odds ratio (OR) 1.80, 95% confidence interval (CI) 1.03, 3.14)] and TSH greater than 10 mU/L (OR 3.95, 95% CI 1.87, 8.37) but not with TSH 2.51–4.5 mU/L (OR 1.09, 95% CI 0.61, 1.93).

Conclusions: The majority of levothyroxine-treated women have early gestational TSH levels above the recommended targets (>2.5 mU/L) with a strong risk of miscarriage at levels exceeding 4.5 mU/L. There is an urgent need to improve the adequacy of thyroid hormone replacement in early pregnancy. **(*J Clin Endocrinol Metab* 99: 3895–3902, 2014)**

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Abbreviations: CI, confidence interval; GPRD, General Practice Research Database; IQR, interquartile range; OR, odds ratio.

Primary hypothyroidism affects 3%–10% of women (1, 2) and is predominantly managed in primary care (3). A substantial proportion of affected individuals are of child-bearing age (1, 2), and approximately 1%–2% of women receive levothyroxine during pregnancy (4). There is an estimated 30%–50% increase in levothyroxine requirements during pregnancy (5, 6), and most hypothyroid women who become pregnant will require an increase in levothyroxine dose, although the optimal magnitude and timing of this increase remains uncertain (4, 6, 7).

Recent reports have highlighted that between 24% and 55% of women established on levothyroxine prior to pregnancy have an elevated (TSH) at their first antenatal visit (8–13). Suboptimal thyroid function is associated with adverse pregnancy outcomes including an increased risk of miscarriage, premature birth, gestational hypertension, placental abruption, and postpartum hemorrhage (14–16) as well as impaired neurological development in the offspring (17, 18). As would be expected, these complications are more common and severe in overt hypothyroidism than in subclinical hypothyroidism (19, 20). A recent systematic review reported that levothyroxine is effective at lowering the risk of preterm delivery [relative risk 0.41, 95% confidence interval (CI) 0.24, 0.68] and miscarriage (relative risk 0.19, 95% CI 0.08, 0.39) in overt hypothyroidism (21).

However, it is currently unclear whether levothyroxine reduces adverse obstetric/offspring outcomes in subclinical hypothyroidism (21, 22). A large randomized controlled trial, the Controlled Antenatal Thyroid Study, showed that correction of maternal subclinical hypothyroidism with levothyroxine did not benefit child cognitive function, although intervention could have been initiated too late in pregnancy (after 12 wk) to be effective (23). Elsewhere intervention with levothyroxine reduced the odds of pregnancy losses in thyroperoxidase antibody-positive women (24), although the duration of treatment was very brief (25). Also, in a large population-based study of untreated antibody-negative women, 6.1% of women with early gestation TSH between 2.5 and 5.0 mU/L had miscarriages compared with 3.6% of those with TSH less than 2.5 mU/L (increment 69%, $P = .006$) (26).

In 2007 The Endocrine Society recommended that hypothyroid women contemplating pregnancy should have their levothyroxine dose adjusted to achieve a preconception TSH less than 2.5 mU/L (27). Additional monitoring and dose titrations are also advised to maintain a TSH between 0.2 and 2.5 mU/L in the first trimester and between 0.3 and 3.0 mU/L in later pregnancy (27). Similar targets have been endorsed by subsequent guidelines (25, 28). However, inadequate treatment of primary hypothyroidism remains a major problem with 40%–48% of hypothyroid patients either overtreated or undertreated (1, 29–31).

To date, there has been no population-based study of pregnancy outcomes in women on long-term levothyroxine. Most studies in this area have been small and in groups of women attending specialist hospital antenatal clinics (8–10, 13). These hospital cohorts are less representative of the general population and might underestimate the incidence of early miscarriages occurring prior to specialist clinic enrollment. In this report we addressed this topic using data from the General Practice Research Database (GPRD), a large, well-validated UK primary care database of more than 5 million individuals from 508 primary care practices throughout the United Kingdom (32). Our aim was to determine the adequacy of thyroid hormone replacement in pregnancy and to examine pregnancy outcomes in relationship to TSH levels.

Subjects and Methods

Cohort

We used data from the GPRD, now called the Clinical Practice Research Datalink (www.cprd.com), and the present study cohort is derived from a data set of 55 501 individuals described previously (31). In brief, these were all women first prescribed levothyroxine between 2001 and 2009 excluding those with a prior history of Graves' disease, thyrotoxicosis, hyperthyroidism, toxic multinodular goiter, solitary toxic nodule, thyroiditis, thyroidectomy, radioiodine use, and pituitary disease/surgery. In this data set 7978 were women of child-bearing age (18–45 y), and from these we identified 1013 pregnancies in women established on levothyroxine for at least 6 months. Our data set thus comprised individuals with primary hypothyroidism alone who were receiving levothyroxine.

Identification of pregnancies and TSH levels

Pregnancies were identified using 987 pregnancy-related codes including pregnancy confirmation tests, antenatal clinic appointments, and delivery records. Codes were used in combination to estimate the date of pregnancy and thereby the timing of TSH tests. For instance codes pertaining to confirmation of pregnancy, early stage of pregnancy, and morning sickness were used to identify first-trimester dates, whereas codes relating to delivery dates and antenatal clinic attendance from 12 to 40 weeks were used to confirm second- and third-trimester dates. Pregnancy dates were linked to date of first levothyroxine prescription, and only a woman's first pregnancy occurring at least 6 months after levothyroxine initiation was included. If individuals had more than one TSH level recorded in a trimester, the highest reading was used. Individuals with evidence of a pregnancy but no evidence of an outcome such as delivery, miscarriage, or termination were excluded from pregnancy outcome analysis (delivery/miscarriage) but not from descriptive analyses of TSH levels during pregnancy. Sensitivity analyses were undertaken with individuals without a delivery outcome (miscarriage/termination aside) recoded as a successful delivery. Insuf-

ficient data on free T_4 levels and thyroid peroxidase antibody titers were available, so these were not analyzed.

Identification of adverse pregnancy outcomes

Adverse pregnancy outcomes were identified using medical codes. For the primary analysis, codes relating to miscarriages and stillbirths were used. For a secondary analysis, other adverse pregnancy complications were identified and grouped together using medical codes, specified a priori covering emergency caesarean section, preeclampsia, postpartum hemorrhage, placental abruption, prematurity, low birth weight, growth restriction, need for intensive care, and neonatal death.

Identification of diabetes and socioeconomic status

Individuals with a diagnosis of type 1diabetes, type 2 diabetes, or gestational diabetes were identified using multiple medical codes pertaining to these conditions and were included only if diabetes preceded or occurred during the pregnancy of interest. Quintiles of socioeconomic status were calculated from the Index of Multiple Deprivation for the postcode of each individual's general practice.

Statistical analysis

Serum TSH is presented as median (interquartile range). TSH was compared according to the year of pregnancy before and after The Endocrine Society guidelines (27) (2001–2007 vs 2008–2009) and by pregnancy trimester (first vs second/third) using the Wilcoxon-rank test. The primary analysis assessed the odds of miscarriage/stillbirth by first-trimester TSH level. Secondary analyses were undertaken to examine the odds of other pregnancy complications by first- and second/third-trimester TSH. To reflect trimester-specific reference ranges as recommended by current international guidelines (25, 28), first-trimester TSH levels were split into five categories: 1) less than 0.2 mU/L; 2) 0.2–2.50 mU/L; 3) 2.51–4.50 mU/L; 4) 4.51–10 mU/L; and 5) greater than10 mU/L. The lower three TSH level categories were subtly different for second/third-trimester analysis: 1) less than 0.3 mU/L; 2) 0.3–3.00 mU/L; and 3) 3.01–4.50 mU/L (26, 27). The 0.2- to 2.5-mU/L and 0.3- to 3.0-mU/L categories represent the recommended optimal ranges for the first and second/third trimesters, respectively, and were used as the reference category for the multivariable model. Analyses were adjusted for age, year of pregnancy, social class, and diabetes before or during pregnancy. All statistical analyses were undertaken using STATA version 12 (STATACORP).

Regulatory approval

Access to the GPRD data set was obtained via the Medical Research Council license.

Results

TSH levels in women of child-bearing age (18–45 y) (n = 7978)

An analysis of the most recent TSH levels of all women aged 18–45 years who had been on levothyroxine for at least 1 year at the time of this TSH measurement revealed a median TSH of 2.22 mU/L [interquartile range (IQR) 0.97–3.78] with 3678 (46.1%) having a TSH greater than 2.5 mU/L and 364 (4.6%) with TSH greater than 10 mU/L. One thousand eighty-two women (13.6%) were overtreated with a TSH less than 0.4 mU/L and 408 women (5.11%) had a TSH less than 0.1 mU/L (Supplemental Table 1).

TSH levels in women who became pregnant (n = 1013)

The median age at conception was 33 years (IQR 29–37) with a median duration of levothyroxine therapy prior to pregnancy of 17.5 months (IQR 11.2–25.8). Of the 1013 pregnancies, we identified 541 deliveries (53.4%), 144 miscarriages (two were stillbirths) (14.2%), 79 terminations of pregnancy (7.8%), 171 pregnancies with no outcome recorded (16.9%), and 78 pregnancies (7.7%) that were ongoing when the data were extracted (before the completion of pregnancy) (Figure 1). No differences were observed between individuals with pregnancy outcomes unaccounted for and those with pregnancy outcomes accounted for with regard to calendar year of pregnancy ($P = .18$), age at pregnancy ($P = .17$), first-trimester TSH level ($P = .17$) or second/third-trimester TSH level

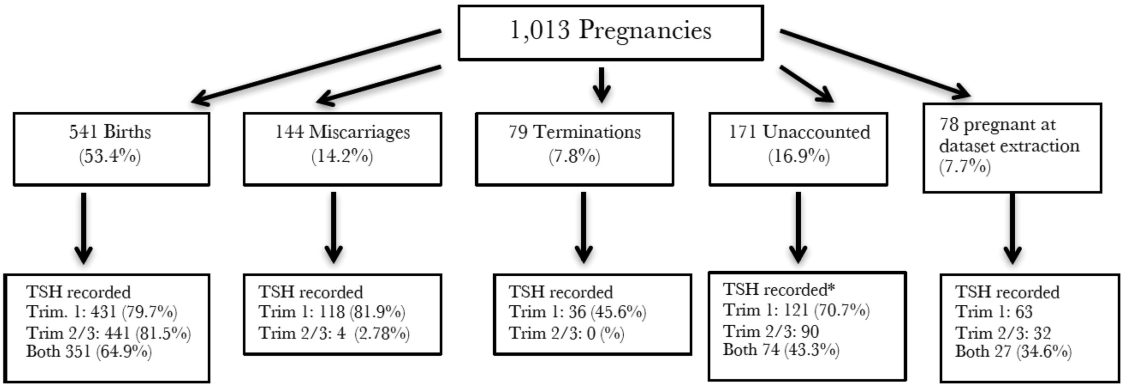

Figure 1. Pregnancy outcomes and TSH measurements in this study.

($P = .73$), presence of diabetes (P = .37), or social class ($P = .23$).

Eight hundred eighty women (86.9%) had a TSH level recorded during pregnancy, whereas 769 (75.9%) had a TSH recorded in the first trimester. Of women with a first-trimester TSH, 483 (62.8%) had levels that were greater than 2.5 mU/L, 224 (29.1%) were greater than 4.50 mU/L, and 57 (7.41%) were greater than 10 mU/L. The spread of first-trimester TSH values by category is shown in Figure 2A. The median TSH in the first trimester was slightly lower before 2007 (2.78 mU/L, IQR 1.33–4.96) than after 2007 (2.98 mU/L, IQR 1.77–5.31) ($P = .09$). A summary of the TSH levels by year-group is shown in Supplemental Table 2.

Five hundred sixty-seven women had TSH measured in the second/third trimester, of which 348 (61.4%) had a TSH within the trimester-specific target range of 0.30–3.0 mU/L. In addition, 168 women (29.6%) had TSH greater than 3.0 mU/L in the second/third trimester and 51 (9.0%) had a TSH less than 0.3 mU/L (Figure 2B). The median TSH levels were lower in the second/third trimester (2.10 mU/L, IQR 1.19–3.37 mU/L) than in the first trimester (2.89 mU/L, IQR 1.50–5.0 mU/L) ($P \leq .0001$). However, inadequate TSH levels persisted in a substantial proportion of pregnancies, and 66.5% of women with TSH greater than 2.5 mU/L in the first trimester who also had a TSH measured in the second/ third trimesters had a second/third-trimester TSH greater than the target of 3.0 mU/L. One hundred thirty-three of the 1013 pregnancies (13.1%) had no corresponding TSH record and more than half of these (51.9%) ended in miscarriage or termination. A small number of women amounting to 20 of the 541 women with a delivery at term recorded (3.7%) had no corresponding TSH measurement over the entire duration of pregnancy and thus did not appear to have had thyroid function measured during pregnancy despite being established on levothyroxine.

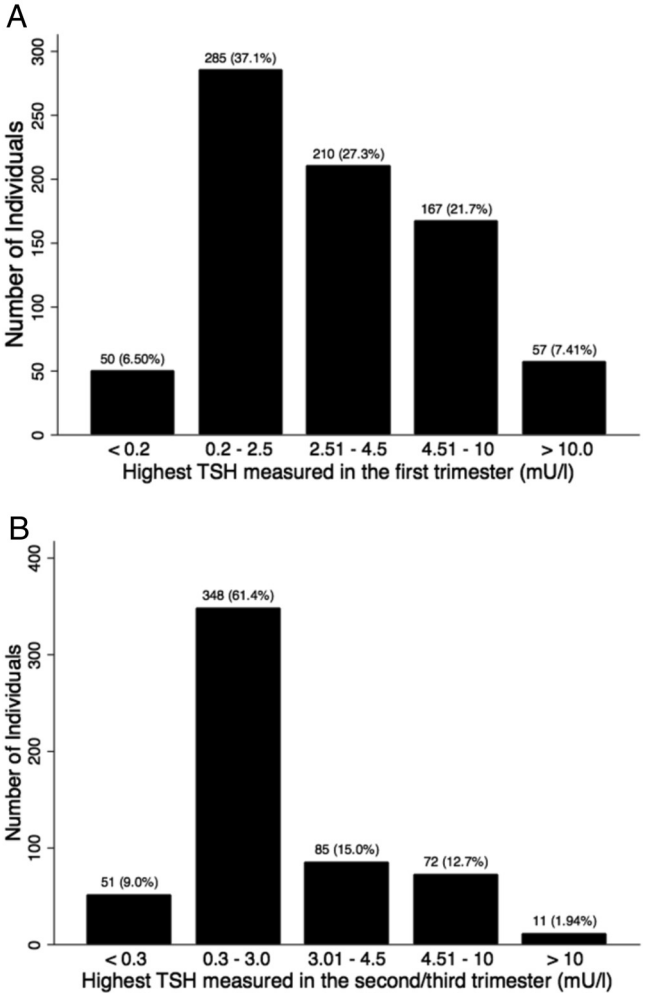

Figure 2. A, Highest recorded TSH levels during trimester 1. Numbers of women in each category are shown above each bar. Percentages are derived from all women with a documented TSH in that category. B, Highest recorded TSH levels during trimesters 2/3. Numbers of women in each category are shown above each bar. Percentages are derived from all women with a documented TSH in that category.

Delivery/miscarriage outcomes by first-trimester TSH

We identified 431 deliveries and 118 miscarriages in the 769 pregnancies of women with a TSH level recorded in the first trimester. In 22 of the 144 total miscarriages (15.3%), the miscarriage was the first GPRD record of a pregnancy and was not preceded by a thyroid function test in pregnancy (Figure 1).

The median first-trimester TSH was higher in women who miscarried than in those with a successful delivery, 3.59 mU/L vs 2.80 mU/L ($P = .003$). After adjusting for maternal age, calendar year, social class and presence of diabetes, the odds of miscarriage rose with increasing TSH levels above the target TSH range of 0.2–2.5 mU/L (P for trend = .008), with the greatest impact observed with TSH levels greater than 10 mU/L [odds ratio (OR) 3.95 (95% CI 1.87, 8.37)] (Table 1). A clear increase in the odds of a miscarriage was also observed with TSH levels between 4.51 and 10 mU/L (OR 1.80, 95% CI 1.03, 3.14). In individuals with TSH 0.2–2.5 mU/L, the risk of a miscarriage was 17%, rising to 30% at TSH greater than 4.5 mU/L and 41.5% at TSH greater than 10 mU/L. Individuals with a maximum TSH less than 0.2 mU/L or TSH 2.51–4.5 mU/L had an OR of miscarriage greater than 1, although this was not significant.

In addition, 60 women had a recorded TSH less than 0.2 mU/L, which did not persist through pregnancy. Analysis of these individuals with transient TSH suppression did not reveal any increase in the odds of miscarriage compared with individuals who never had had a TSH outside

Table 1. Odds of Miscarriage by First-Trimester Serum TSH Level

TSH, mU/L	Total, n	Miscarriages, n	Percentage Miscarried	Unadjusted Odds of Miscarriage	95% CI	*P* Value[a]	Adjusted Odds of Miscarriage[b]	95% CI[b]	*P* Value[a,b]
<0.2	36	6	16.7	0.97	0.37, 2.51		1.14	0.62, 1.93	
0.2–2.5	199	34	17.1	1.00		.02#	1.00		.008#
2.51–4.5	151	29	19.2	1.15	0.66, 2.00		1.09	0.61, 1.93	
4.51–10	122	32	26.2	1.73	1.00, 2.98		1.80	1.03, 3.14	
>10	41	17	41.5	3.44	1.66, 7.08		3.95	1.87. 8.37	

There were 549 individuals in the model: 431 deliveries and 118 miscarriages. The reference category is the recommended first-trimester TSH: 0.2–2.5 mU/L.

[a] Test for trend comparing the odds of miscarriage by TSH levels above 2.5 mU/L to the reference category of 0.2–2.5 mU/L.

[b] Adjusted for age, calendar year of pregnancy, diabetes during or before pregnancy, and social class.

the trimester-specific target range [OR 0.62 (95% CI 0.25, 1.54) $P = .30$]. Sensitivity analyses with all unidentified pregnancy outcomes recoded as a successful delivery revealed similar associations (Supplemental Table 3). Analyses stratified by age revealed that in women aged younger than 35 years, suboptimal thyroid function was associated with higher risk estimates of miscarriage than in women aged 35 years or older. However, this is likely related to the higher baseline risk of miscarriage in the older population (Supplemental Table 4) because likelihood tests for interaction by age were not significant ($P = .15$).

Odds of other adverse pregnancy outcomes by first-trimester and second/third-trimester TSH

Out of the 431 births with a TSH level measured in the first trimester, 29 (6.73%) had other adverse pregnancy outcomes. Of the 441 births with a TSH level measured in the second/third trimester, 31 (7.0%) had other adverse pregnancy outcomes. There was no clear pattern of association with adverse events around delivery and TSH level in the first trimester or second/third trimester (Supplementary Tables 5 and 6), although individuals with a TSH level in the target ranges had the lowest odds of a late adverse pregnancy outcome.

Discussion

Our study shows that almost half of women of reproductive age who take levothyroxine for primary hypothyroidism have a thyroid status that is not optimal for pregnancy according to current guidelines. Furthermore, up to 60% of pregnant women have suboptimal TSH levels in early pregnancy. In addition, we found no evidence of improvement in gestational thyroid hormone replacement since The Endocrine Society guidelines were introduced in 2007. Our findings are in keeping with recent regional data from Scotland (11) and Wales (13) and suggest that the current problem is widespread and persistent. This is an important issue to address because we also observed in our cohort that TSH levels above 2.5 mU/L in the first trimester were associated with an increased odds of miscarriage, with levels between 4.51 and 10 mU/L having almost double and levels greater than 10 mU/L nearly a 4-fold increase in the odds of subsequent miscarriage, even after adjusting for key confounders. In effect, women with TSH levels within the current guideline targets (0.2–2.5 mU/L) had the lowest miscarriage rates (17%), similar to that of the UK general population (20%) (33). It would therefore seem reasonable that the currently recommended preconception and early gestation TSH targets (<2.5 mU/L) are maintained.

Although we observed a trend toward increasing odds of miscarriage with rising TSH above 2.5 mU/L, we did not find a significant increase in the odds of miscarriage in women with TSH levels of 2.51–4.5 mU/L. This finding is in contrast to the large population-based study by Negro et al (26), which reported an increased risk of miscarriages at TSH levels of 2.5–5.0 mU/L. In addition, the miscarriage risk in our study in women with a TSH of 2.5–4.5 mU/L was higher than that observed by Negro et al in women with a comparable TSH of 2.5–5.0 mU/L (19% vs 6%). The reasons for these differences are unclear, but the higher miscarriage rates in our sample may have arisen because the study by Negro et al was restricted to antibody-negative women, whereas our patients were older (median age 33 y vs 28 y) and more likely to be antibody positive from Hashimoto's thyroiditis, all factors that are known to increase the risk of pregnancy loss (24). Furthermore, our study may have been underpowered to detect an effect within this TSH category.

Our data also indicate the need for a more meticulous approach to thyroid hormone replacement in pregnancy. Approximately 13% of pregnant women in our cohort did not have a TSH level measured throughout pregnancy,

highlighting the need for closer monitoring. Another important observation was that transient TSH suppression did not carry an increased risk of miscarriage, suggesting that brief periods of overreplacement were not detrimental to obstetric outcomes and should not deter judicious increases in levothyroxine dose to attain target TSH levels. However, larger observational studies are needed to better define optimal TSH levels in the first trimester.

We also identified a worrying discrepancy between published guidelines and clinical practice. The reason for this is likely to be multifactorial including a lack of familiarity among clinicians with the current Endocrine Society guidelines (34), high rates of unplanned pregnancies (33), noncompliance with levothyroxine (35), and inconsistencies in management strategies among endocrinologists and obstetricians (36). Optimization of early gestation thyroid function in women on levothyroxine is achievable. One approach is to increase the levothyroxine dose by two extra tablets a week on conception, representing an approximate dose increase of 30% (7). This appears to be safe and effective but requires wider dissemination of the guidance and a willingness on the part of individual women to independently adjust their doses. A second strategy (37) is to ensure that preconception TSH is maintained in the low-normal range (<1.2 mU/L) to increase the likelihood of optimal thyroid status in early gestation (37). However, close monitoring will be required to prevent overtreatment, which was seen in only 5.1% of our sample based on a TSH less than 0.1 mU/L according to the American Thyroid Association pregnancy guidelines (28). Subclinical hyperthyroidism has not been shown to be harmful in pregnancy (38), and the small risk of its occurrence is largely outweighed by the adverse effects of suboptimal replacement due to insufficient or late dose increases.

When compared with the risks of undertreatment, the benefits of levothyroxine optimization were substantial: 21 of the 49 miscarriages occurring at TSH levels greater than 4.50 mU/L (42.9%) may have been prevented if they had the same rate of miscarriage as individuals with a TSH level between 0.2 and 2.5 mU/L. Thus, our findings are also relevant to the current debate on universal thyroid screening. If levothyroxine therapy can reduce the risk of miscarriage in women with TSH levels above 4.5 mU/L to that observed in 0.2–2.5 mU/L, then there would be substantial gains at the population level from thyroid screening.

The strengths of the current study are the use of a large, well-validated, population-based data set with detailed clinical and biochemical data collected over a long period. The widespread use of electronic prescriptions by UK primary care physicians makes it unlikely that individuals receiving levothyroxine were missed. Similarly, almost all laboratories in England were issuing electronic biochemical results by the year 2000; thus, very few TSH results would have been excluded. Compared with studies based on hospital clinic records, our data set included data from a wide variety of practitioners and is therefore representative of the general population. In addition, we could identify early pregnancy losses that would have been missed in hospital-based studies because most pregnant women do not enroll in hospital antenatal clinics until well into gestation. Indeed, 15.3% of our identified miscarriages were the first entry of that pregnancy into the GPRD record, and these events would certainly have been missed using hospital clinic records alone. Also, because our study is several times larger than previous studies, we were able to identify a substantially greater number of miscarriages, enabling us to better define risks according to TSH thresholds. Of practical importance is the longitudinal nature of our study, which has highlighted the persistent nature of the problem despite published guidelines (27). Finally, the use of observational data has allowed us to quantify the relative risks of over- and undertreatment of gestational hypothyroidism, which could not have been satisfactorily addressed in a nonobservational study design.

Our study limitations include the lack of data on some potential confounding factors, most notably obstetric comorbid conditions. Thus, our observed associations between TSH levels and adverse obstetric outcomes could have been influenced by other undetermined obstetric factors. Furthermore, we could have miscalculated the residual confounding from social class by linking this to the patient's primary care practice rather than individual addresses, which were unavailable to us. We also lacked data on free T_4 levels and thyroid peroxidase antibody titers, and therefore, we were unable to clarify the impact of hypothyroxinemia and thyroid autoimmunity on the outcomes observed in this study. Lastly, we were unable to identify 17% of pregnancy outcomes, which could have potentially led to ascertainment bias. It is, however, likely that the vast majority of unidentified outcomes result in normal deliveries because adverse outcomes are more likely to be recorded. A sensitivity analysis assuming all unidentified outcomes were normal deliveries revealed similar results (Supplemental Table 3).

In conclusion, most levothyroxine-treated women in this community-based cohort have early gestational TSH above the currently recommended targets. The best pregnancy outcomes were seen in women with target TSH

levels, and a strong risk of miscarriage was present at TSH levels exceeding 4.5 mU/L. There is therefore a pressing need for better liaison between endocrinologists and primary care practitioners to improve the adequacy of thyroid hormone replacement in pregnancy or preferably before conception.

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