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Full length article

Temporal trends in thyroid-stimulating hormone and live birth rate in subclinical hypothyroid patients in a recurrent pregnancy loss population

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ABSTRACT

Objectives: The purpose of this study was to explore if thyroperoxidase antibody positivity impacts thyroid stimulating hormone levels during pregnancies following the index visit and how live birth rate is impacted when treated subclinical hypothyroidism is treated with levothyroxine or not.

Study design: A retrospective chart review of 1443 recurrent pregnancy loss patients from BC Women's Hospital recurrent pregnancy loss clinic was conducted. Thyroid stimulating hormone in pregnancies after the index visit across thyroperoxidase antibody status was analyzed using mixed-effects linear regression. Live birth rate in patients with subclinical hypothyroidism (thyroid stimulating hormone 2.5–10 mIU/L) with levothyroxine treatment was compared to those without relative to euthyroid patients using logistic regression.

Results and conclusions: There was no significant difference in patient demographics including age, body mass index, or number of previous live births or pregnancy losses between groups. The distribution of recurrent pregnancy loss causes between groups revealed no difference in proportion of patients with anti-phospholipid antibody syndrome, hereditary thrombophilia, hyperprolactinemia, or anatomic causes. There was no significant change in thyroid stimulating hormone across thyroperoxidase antibody or treatment status ($p = 0.24$) for up to four subsequent pregnancies. An increased live birth rate in subclinical hypothyroidism when treated with levothyroxine relative to untreated (OR = 2.25, $p < 0.001$) was seen.

Thyroid stimulating hormone values do not change over time following the index visit for up to 4 subsequent pregnancies irrespective of the thyroxperoxidase antibody status. An increase in live birth rate was found in patients with borderline subclinical hypothyroidism when treated with levothyroxine.

Introduction

Of all pregnancies, there is a 15 % rate of miscarriage [1]. <5 % of patients experience two or more pregnancy losses and are considered part of the recurrent pregnancy loss (RPL) population [2,3]. Pregnancy loss is defined as losses before the 20th week of gestation and excludes molar and ectopic pregnancies. RPL patients are often referred to a clinic to investigate the possible causes of pregnancy loss including anatomic, genetic, autoimmune, and endocrine problems [2].

Hypothyroidism is a possible endocrine cause [4]. Under normal conditions, the thyroid gland uses iodine to create triiodothyronine (T3) and thyroxine (T4). They act on tissues to regulate metabolism, heart rate, and body temperature [5]. Hypothyroidism in the general population is associated with cold sensitivity, fatigue, and muscle cramps [6]. In pregnancy, demand for thyroid hormone increases [7]. The thyroid gland can increase 10 % in size in regions with adequate iodine nutrition and up to 40 % in areas with iodine-poor diets [7]. Thyroid hormone is important in early pregnancy especially, up to the 13th week of gestation, while the fetus relies solely on maternal thyroid hormone [8]. Without sufficient thyroid hormone, the rate of pregnancy loss increases [9].

To help determine possible causes of the RPL, thyroid stimulating

Abbreviations: BMI, body mass index; LBR, live birth rate; RPL, recurrent pregnancy loss; SCH, subclinical hypothyroidism; T4, thyroxine; T3, triiodothyronine; TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone.

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hormone (TSH) levels are measured. A TSH above 10 mIU/L indicates clinical hypothyroidism and is determined to be a cause of RPL [10]. Patients with subclinical hypothyroidism (SCH) (TSH 2.5–10 mIU/L) are deemed to have unexplained RPL unless another cause is found [10]. Yet, patients with TSH > 4 mIU/L have been shown to have improved pregnancy outcomes when treated with levothyroxine [10,11].

Thyroid autoimmunity may be a cause of hypothyroidism so thyroid peroxidase antibody (TPOAb) is measured in RPL investigations [4]. Studies have found that patients with positive TPOAb have higher TSH levels [12]. An association has been found between thyroid autoimmunity and RPL [13]. Evidence suggests those with positive TPOAb without hypothyroidism do not have a reduced rate of miscarriage when treated with levothyroxine [13–15]. Normally, TSH increases very minimally in patients ages 18–65 [16]. In the population with positive TPOAb, it is likely that TSH would rise over time in the pathogenesis of hypothyroidism. In the RPL population, this has not been explored.

A study examining the RPL population found levothyroxine is most successful at improving the rate of pregnancy reaching >10 weeks in patients with a TSH > 4 mIU/L [17]. It is unclear if this is also the case for the live birth rate (LBR) in this population or if initiating levothyroxine at TSH > 2.5 mIU/L improves pregnancy outcomes.

A retrospective cohort study of patients who attended the BC Women's Hospital Recurrent Pregnancy Loss clinic was conducted to address these gaps in knowledge. Because studies have not yet examined how TSH changes over successive pregnancies in the RPL population, this study aimed to examine how TPOAb status impacts how TSH changes over time. Analysis of LBR between patients with SCH with and without levothyroxine was performed.

Materials and methods

Subject inclusion

Retrospective chart review for patients who were assessed at the Recurrent Pregnancy Loss Clinic at BC Women's Hospital in Vancouver, Canada from January 2011 to July 2019 was conducted. Patients were referred to the clinic and were considered to have RPL after having two or more pregnancy losses prior to 20 weeks gestation [18]. Both visualized and non-visualized pregnancies were included. All patients attending the clinic were screened for potential causes of RPL. 1779 patient charts were reviewed. Duplicates and non-RPL patients were removed leaving 1443 unique patients (Fig. 1). Exclusion criteria

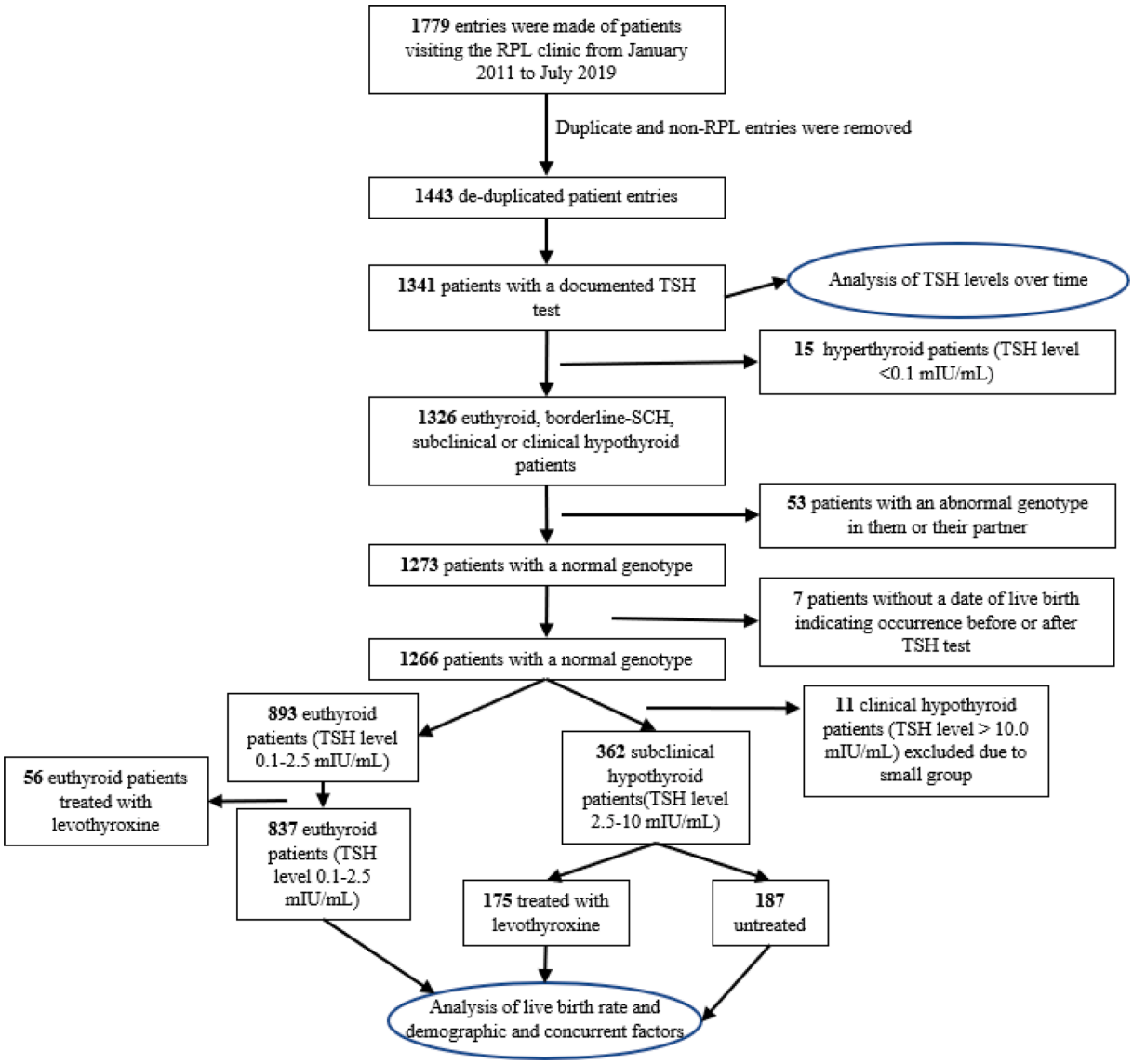

Fig. 1. Flow chart of subject inclusion in the study. (RPL = recurrent pregnancy loss; TSH = thyroid stimulating hormone; borderline-SCH = borderline subclinical hypothyroidism).

extended to patients without a TSH test done, with abnormal karyotypes in either partner, or without a known date of live births (Fig. 1).

Concurrent contributors to RPL

Tests that were performed could, but did not always, include parental karyotyping, tests for endocrine causes, screens for acquired and congenital thrombophilias, assessment of anatomy by hysteroscopy, or hysterosalpingogram, and tests for autoimmune conditions. Tests were deemed to be positive according to thresholds from regional laboratories. Patients were deemed to have contributing hereditary thrombophilia factors if a test was positive for prothrombin or factor V Leiden mutation, or for protein C or protein S deficiencies (<0.7 IU/mL). Lupus anticoagulant, anticardiolipin antibodies and B2 glycoprotein-1 were used to assess for antiphospholipid antibody syndrome where indicated. Patients were determined to have hyperprolactinemia if a prolactin test was elevated above the cut-off on two occasions.

Criteria for thyroid disease

Patients with hypothyroidism were stratified based on severity according to the guidelines for thyroid disease in pregnancy [7]. Clinical hypothyroidism was defined as having a TSH > 10 mIU/L. SCH was defined as having a TSH 2.5–10 mIU/L. Patients who only had TSH 0.1–2.5 mIU/L were deemed to be euthyroid and below 0.1 mIU/L were hyperthyroid. Clinical hypothyroid patients were excluded due to the small number of cases. In patients with multiple TSH tests done, only the highest level was considered. Any patients without a TSH test performed were excluded. Because T3 and T4 are not routinely measured for patients, data on these values was not collected.

In patients with a TPOAb test, a level >35 IU/mL was considered a positive test. This threshold was set by the provincial laboratory in British Columbia. TSH and TPOAb tests were performed routinely in provincially licensed laboratories on a wide scale following Health Canada guidelines.

Treatment

Patients with TSH over 2.5 mIU/L were offered levothyroxine preconception. Patients who were euthyroid but who were treated with levothyroxine were excluded from the analysis of LBR as these patients may have had a history of hypothyroidism not documented in the medical record. Preconception dosing of levothyroxine therapy was based on the TSH. Starting doses were 25, 50, and 75 mcg daily when the TSH was 2.5–4, 4–10 and > 10 mIU/L, respectively. Repeat TSH assays were performed 4–6 weeks after initiating treatment and dosing was adjusted accordingly. TSH was measured again with positive pregnancy test and further levothyroxine dose adjustment was implemented during the first trimester. TSH assay was repeated once every trimester. Thyroxine dose was adjusted accordingly per the treating physician. Patients were also treated for other causes of RPL as appropriate.

Live birth rate

The number of live births was recorded for each patient in each TSH category according to medical records. Only live births that occurred after an initial TSH test were used in analysis. Still births were not included. Pregnancies that resulted in multiple offspring (eg. twin births) were counted as multiple live births.

Temporal trends in TSH levels

TSH values from tests that were performed with each pregnancy, after the initial TSH test, were included in temporal analysis. Pregnancy number, after the initial TSH test, was calculated from medical records, regardless of the pregnancy outcome.

Data analysis

Means and standard deviation, or medians and interquartile ranges, were employed for descriptive statistics. Wilcoxon rank sum test was used for comparing continuous variables. Fisher's exact tests were used to compare categorical variables across groups, including concurrent factors for RPL.

In analysis of TSH values over time, mixed-effects linear regression was used to account for repeated testing on the same patient. Interaction between pregnancy number and TSH across TPOAb positivity and treatment status was analyzed. Non-significant ($p < 0.05$) interaction terms were removed from the model to allow for estimates for main effects where applicable.

In determination of LBR across TSH status categories, logistic regression, controlling for the age at the index visit and length of time since index visit, was used. Any significant comparisons were followed up with post-hoc pairwise tests.

Ethical approval

The study was approved by the University of British Columbia, Children's and Women's Research Ethics Board on 15 July 2020 (reference number H170- 2291).

Results

Patient demographics

A TSH test value was available for 1341 of the 1443 patients whose charts were reviewed. Of those patients, 15 had a TSH below 0.1 mIU/L indicating hyperthyroidism and were excluded. 53 patients were excluded due to an abnormal karyotype in either partner (Fig. 1). Of the remaining 1273 patients, 7 were excluded due to a missing live birth date. 70.5 % (893/1266) of the remaining patients were euthyroid, 28.6 % (362/1266) were SCH, and 0.9 % (11/1266) patients were clinical hypothyroid (Table 1). 56 patients were further excluded from the analyses of LBR because their TSH placed them in the euthyroid category, but they had been treated with levothyroxine, indicating that it was likely they had previous undocumented hypothyroidism that they had been treated for, leaving 837 untreated euthyroid patients.

The baseline demographics revealed that there was no significant difference in age, number of previous pregnancy losses or previous live births, percentage with primary RPL, or body mass index (BMI) between thyroid-status groups (Table 1).

The prevalence of TPOAb positivity was 12.3 % (93/758) across all groups but varied with thyroid status. It was 5.9 % (29/495) in the euthyroid group, 24.3 % (64/263) in the SCH group (Table 1). This difference was found to be significant ($p < 0.0001$). Significant differences were also shown between thyroid status groups in the TSH ($p < 0.0001$), and TPOAb titre ($p < 0.0001$) (Table 1). Mean TSH in the SCH group was 2.9 ± 1.2 mIU/L and 1.4 ± 0.5 mIU/L in the euthyroid group ($p < 0.0001$) (Table 1).

Concurrent factors contributing to RPL

Testing for concurrent factors was not completed for all patients; 777 euthyroid, and 341 SCH patients were investigated for at least one concurrent factor (Table 1). Many patients were also found to have at least one other factor contributing to RPL including 167 (21.5 %) euthyroid and 87 (25.5 %) SCH patients ($p = 0.14$).

Anti-phospholipid antibody syndrome was identified in 8.2 % (52/634) of euthyroid patients and 8.7 % (24/277) of SCH patients ($p = 0.80$) (Table 1). Hyperprolactinemia was found in 2.9 % (16/552) of euthyroid patients 3.8 % (10/258) of SCH patients who completed a prolactin test ($p = 0.52$) (Table 1). Anatomic factors contributing to RPL showed no significant difference between thyroid status groups ($p =$

Table 1
Demographic factors and causes of recurrent pregnancy loss across patients in different thyroid status groups in the recurrent pregnancy loss population.

		Euthyroid (n = 837)	Subclinical Hypothyroidism (n = 362)	P-value
Age (years)	Mean (SD)	34.8 (4.8)	34.4 (4.7)	0.23
Body mass index (kg/m^2)	Mean (SD) (n = sample size)	25.1 (5.4) (n=441)	25.4 (6.2) (n=192)	0.99
No. previous pregnancy losses	Mean (SD)	2.5 (1.3)	2.4 (1.4)	0.15
No. previous live births	Mean (SD)	0.5 (0.7)	0.5 (0.8)	0.19
	Median (25 % quantile, 75 % quantile)	0 (0,1)	0 (0,1)	
% with primary recurrent pregnancy loss (no previous live births)		57.5 % (n = 481)	62.4 % (n = 226)	0.12
Baseline TSH level (mIU/l)	Mean (SD)	1.4 (0.5)	2.9 (1.2)	<0.0001
TPO antibody status	Positive (>35 IU/mL)	3.5 % (n = 29)	17.7 % (n = 64)	<0.0001
	Negative (<35 IU/mL)	54.1 % (n = 453)	55.0 % (n = 199)	
	Unknown	42.4 % (n = 355)	27.3 % (n = 99)	
TPO antibody titre (IU/mL)	Mean (SD)	14.8 (35.1) (n = 495)	65.0 (146.9) (n = 263)	<0.0001
	Median (25 % quantile, 75 % quantile)	9.0 (1.0, 13.0)	11.0 (5.0, 34.0)	
Abnormal factors				
	Any	21.5 % (n = 167/777)	25.5 % (n = 87/341)	0.14
Endocrine factors				
Hyperprolactinemia		2.9 % (n = 16/552)	3.9 % (n = 10/258)	0.52
Autoimmune factors				
Anti-phospholipid antibody syndrome		8.2 % (n = 52/634)	8.7 % (n = 24/277)	0.80
Anatomical factors				
	Any abnormal anatomy	19.1 % (n = 89/466)	23.1 % (n = 54/234)	0.23
	Fibroids	9	4	
	Adhesions	30	7	
	Mullerian abnormality	11	6	
	Polyps	13	15	
	Other	27	24	
Hereditary thrombophilias				
	Any thrombophilia factors	16.7 % (n = 38/228)	14.2 % (n = 16/112)	0.64
	Protein C deficiency	4	1	
	Protein S deficiency	21	12	
	Factor V Leiden	9	5	
	Prothrombin mutation	8	2	

0.23) with 19.1 % (89/466) in euthyroid patients and 23.1 % (54/234) in SCH patients (Table 1). Hereditary thrombophilia factors contributing to RPL were identified in 16.7 % (38/228) of euthyroid patients and 14.3 % (16/112) of SCH patients (p = 0.64) (Table 1).

TSH levels over time

TSH across pregnancies were not found to have a significant association with pregnancy number (p = 0.24) (Fig. 2). TSH also did not interact significantly with TPOAb status or levothyroxine status (Fig. 2). Though, patients with TPOAb positivity were more likely to receive levothyroxine (p = 0.02). In TPOAb negative patients, those that were receiving levothyroxine had a higher TSH on average than their untreated counterparts (p = 0.0004). In TPOAb positive patients, there was no significant difference in average TSH of the treated patients compared to the untreated (p = 0.30).

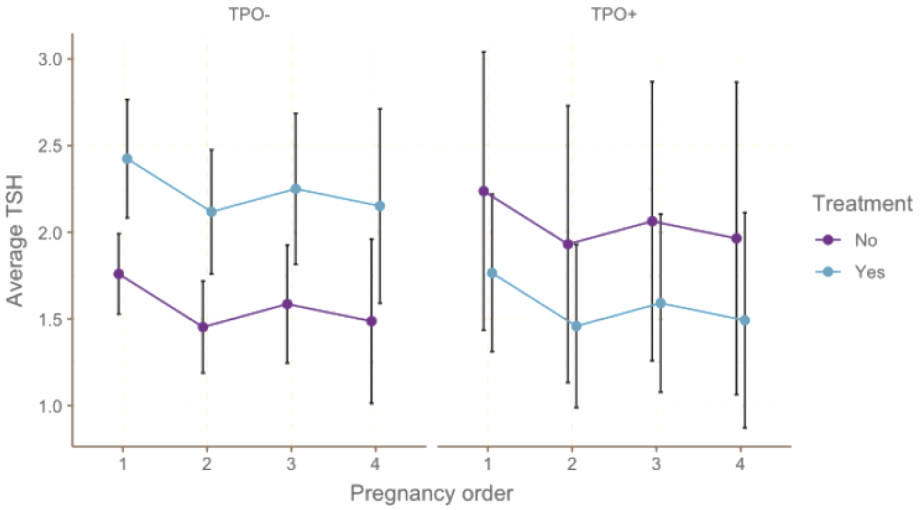

Fig. 2. Average TSH across pregnancies for TPO antibody and levothyroxine treatment status. Patients were considered TPO antibody positive if a value above 35 IU/mL was identified. No significant interaction between pregnancy number and either TPO antibody status or levothyroxine treatment status was identified (p = 0.24). (TSH = thyroid stimulating hormone; TPO = thyroperoxidase).

Live birth rate across thyroid status categories

There was a significant difference between thyroid status groups for the odds of a live birth after TSH test ($p < 0.0001$) (Fig. 3). Compared to the untreated patients (N = 187), when treated with levothyroxine (N = 175), SCH patients had higher odds of a live birth (OR = 2.25, 95 % CI = 1.46 to 3.50) (Fig. 3).

Discussion

The prevalence of SCH in the present RPL cohort was higher than the prevalence that had been reported in the general population and the RPL population [19–21]. SCH was found in 27.0 % of patients included in the study, where 15–20 % had been previously found [19–21].

In this cohort, 12.3 % (93/758) of patients had TPOAb positivity (Table 1). In studies that used a similar threshold of 35–40 IU/mL TPOAb, a similar prevalence of 10–15 % TPOAb positivity has been reported in RPL patients [22–23]. In the current study, higher rates of TPOAb positivity were found in patients with SCH. This has also been found in other studies where TPOAb positivity was shown to be associated with higher TSH and higher rates of hypothyroidism [24–26].

In this study, no significant association was found between levothyroxine status, TPOAb status, and TSH over time (Fig. 2). This suggests that TSH does not change differently over time when a patient is treated with levothyroxine nor when positive for thyroid autoimmunity. The lack of significance might be in part due to the low number of patients that meet criteria for TPOAb positivity. Yet, a similar result was found in a study that compared the number of TPOAb positive patients who developed clinical hypothyroidism depending on their TSH [27]. Only 12 % of TPO positive subjects with a TSH $\leq$ 2.5 mIU/L developed hypothyroidism compared to 55.7 % of TPO positive subjects with a TSH between 2.5 and 4 mIU/L [27]. This suggests that TPOAb positivity is not a sufficient indicator to initiate levothyroxine if a patient is not yet hypothyroid as their TSH may not change over time.

Analysis of LBR across thyroid status categories and levothyroxine status revealed that untreated SCH was significantly associated with lower LBR relative to treated SCH patients (Fig. 3). This suggests that SCH reduces the likelihood of live birth. Previous studies have found similar results suggesting that SCH increases risk of sporadic pregnancy loss [10,20,21,28,29].

For the SCH group, treatment with levothyroxine significantly improved LBR relative to the euthyroid group (Fig. 3). This suggests levothyroxine could be initiated when a TSH > 2.5 mIU/L is identified. This is contrary to what was found by Leduc-Robert et al. where levothyroxine was not shown to improve pregnancy continuation past 10 weeks in RPL patients with TSH 2.5–4 mIU/L [17]. Other studies have suggested that initiating treatment in patients with TSH > 2.5 mIU/L improves pregnancy outcomes when patients are TPO antibody positive only [30]. Thus, testing both TSH and TPOAb status when looking for treatment for RPL is the current recommendation [31].

The current study exhibited strength in its large sample size allowing for large comparison groups. Between patient groups, similar ages, BMI, number of previous pregnancy losses, prevalence of primary RPL, and concurrent factors contributing to RPL were found (Table 1).

Due to the small number of patients in the clinical hypothyroid group in this study, analysis and thus conclusions could not be extended to that group. As well, the small number of patients with TPOAb positivity may have impeded the significance of the TPOAb levels over time between groups. Sample size calculations were not conducted prior to beginning this study. Future research directions could include similar studies where more patients from these groups are included.

In conclusion, in a cohort of RPL patients, TSH was not found to vary significantly over time regardless of TPOAb status or levothyroxine status. This indicates that TPOAb positivity should not be used alone to determine whether levothyroxine is necessary as hypothyroidism is not guaranteed to occur.

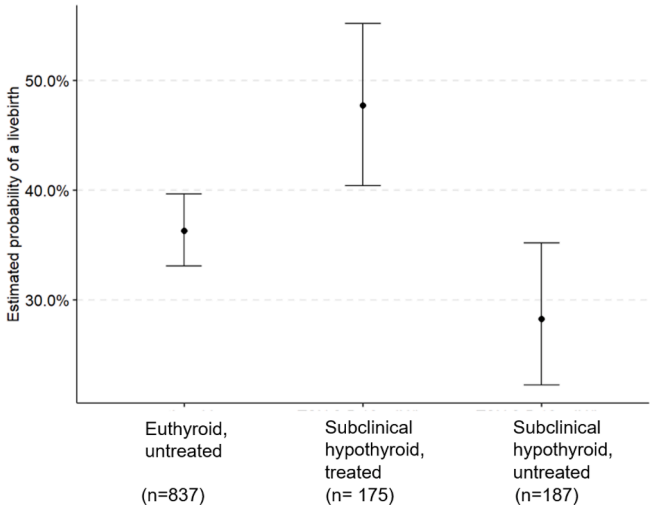

Fig. 3. Predicted probability of a live birth across thyroid status categories with or without levothyroxine treatment. Error bars indicate 95 % confidence intervals. (Borderline-SCH = borderline subclinical hypothyroidism).

Also, analysis suggested LBR was significantly lower in untreated SCH patients compared to those that were treated with levothyroxine.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mohamed A. Bedaiwy is on the advisory board for AbbVie and Baxter and has received research grant funding from Ferring.

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