A Comparison of the Maternal and Perinatal Outcomes of Pregnant Patients who are Euthyroid versus those with Subclinical Hypothyroidism Treated with Levothyroxine Using Different TSH Cut-off Levels

Mae Rhea Lim-Pacoli, M.D.*; Ceryl Cindy Tan, M.D.*; and Imelda L. Bilocura, M.D.*

Abstract

Introduction: In 2017, the American Thyroid Association (ATA) revised their guidelines that when trimester and assay specific TSH reference intervals is unavailable, a TSH cut-off of 4.0 mIU/L replacing the previously recommended 2.5-3.0 mIU/L may be used to define maternal hypothyroidism. It states that levothyroxine treatment is considered if anti-TPO levels are elevated and TSH is between 2.5 mIU/L and the trimester-specific upper limit. These recommendations are a major departure from our current practice because the local TSH trimester-specific reference interval is not applicable due to a different assay used and the anti-TPO result is not readily available.

In this population-based study, we aimed to determine and compare the maternal and perinatal outcomes of pregnant women who are euthyroid (TSH 0.3-2.4 mIU/L) versus those with subclinical hypothyroidism at different TSH cut-off levels (TSH 2.5-4.0 mIU/L, TSH 4.0-10.0 mIU/L) treated with levothyroxine.

Methods: This is a single-center, prospective cohort study conducted at Chong Hua Hospital, Cebu City from September 2017 to September 2018 where a total of 505 pregnant women qualified. The cohort was divided into three groups: the euthyroid group of 404 women with TSH 0.3-2.4 mIU/L as control subjects; 101 women with subclinical hypothyroidism treated with levothyroxine further subdivided into TSH level 2.5-4.0 mIU/L (81 women) and TSH level >4.0-10.0 mIU/L (20 women). These patients were followed through to delivery to document and compare the maternal and perinatal outcomes versus euthyroid patients.

Results: There was no statistically significant difference among the group of patients with subclinical hypothyroidism treated with levothyroxine versus euthyroid patients in documented complications of pregnancy, such as GDM, gestational HPN, pre-eclampsia, PROM, low APGAR score and fetal distress. However, in patients with baseline TSH 2.5-4.0 mIU/L there was preterm delivery in six (7.41%) patients, post-term delivery in two (2.5%) patients, with seven (8.6%) small for gestational age (SGA) infants and two (2.5%) large for gestational age (LGA) infants. In patients with baseline TSH > 4.0-10.0 mIU/L, preterm delivery occurred in two (10%) patients.

In secondary analysis adjusted for age and parity at enrolment, pregnant women treated with levothyroxine at baseline TSH 2.5-4.0 mIU/L and TSH > 4.0-10.0 mIU/L versus the untreated women with TSH < 2.5 mIU/L showed no difference in the maternal and perinatal outcomes of pregnancy measured.

Conclusion: This study has shown a 12.5% prevalence of subclinical hypothyroidism in our setting. There was no difference in the maternal and perinatal outcomes of pregnant patients who are euthyroid versus those with subclinical hypothyroidism treated with levothyroxine at a TSH threshold of 2.5-4.0 mIU/L and >4.0-10.0 mIU/L. These findings support the view that levothyroxine treatment in pregnant women with subclinical hypothyroidism at a TSH cut-off of 2.5 mIU/L shows no harmful effects.

Keywords: pregnancy, subclinical hypothyroidism, treatment outcome

Introduction

In the setting of pregnancy, maternal hypothyroidism is defined as a thyroid stimulating hormone (TSH) concentration elevated beyond the upper limit of the pregnancy-specific range. There is a wide variation in the prevalence of hypothyroidism in pregnancy – 2.5% in the West to 13.5% in India.[1,2,3] It has been associated with multiple pregnancy-related adverse outcomes in many, but not all, observational studies.[4,5,6] A meta-analysis of 18 cohort studies found that pregnant women with untreated subclinical hypothyroidism are at higher risk for pregnancy loss, placenta abruption, premature rupture of membranes, and neonatal death compared with euthyroid women.[7]

In view of this, at the obstetric outpatient charity services of Chong Hua Hospital, the investigation of thyroid dysfunction is considered in routine screening protocols of pregnant women, leading to an increase in referrals to the endocrinology section.

* *Section of Endocrinology, Diabetes and Metabolism, Chong Hua Hospital, Cebu City*

Corresponding author: Mae Rhea Lim-Pacoli, M.D., Chong Hua Hospital, Cebu City, Philippines
Email: maepacoli@gmail.com

In terms of management, many endocrinologists have prescribed levothyroxine therapy for women with subclinical hypothyroidism in pregnancy. This is further supported by an underlying belief that levothyroxine therapy is physiologic and harmless. However, emerging data have demonstrated increased risks of pre-eclampsia, small for gestational age (SGA) neonates, preterm delivery, gestational diabetes and lower IQ.[7,8]

In 2017, the American Thyroid Association (ATA) revised their guidelines and emphasized that trimester and assay specific TSH reference intervals should ideally be defined in thyroid antibody negative pregnant women with optimal iodine intake and without thyroid illness. Importantly, when this is unavailable, a TSH cut-off of 4.0 mIU/L replacing the previously recommended 2.5-3.0 mIU/L may be used to define maternal hypothyroidism.[9]

The guidelines lack clarity as when to start levothyroxine, which is a time sensitive decision. Instead, a treatment algorithm is provided based on the presence or absence of antibodies to thyroid peroxidase (anti-TPO). The guidelines state that levothyroxine treatment is considered if anti-TPO levels are elevated and TSH is between 2.5 mIU/L and the trimester-specific upper limit.[9] However, given that anti-TPO antibody status is not routinely tested when TSH is taken, a subsequent blood test for anti-TPO will be required for many pregnant women which could cause a potential delay in treatment and an increase in the pathology and consultation costs. Patal, et al. has established a trimester-specific reference interval for thyroid function tests in pregnant Filipino women.[10] However, the assays used in the study were immunoradiometric assay (IRMA) and radioimmunoassay (RIA), which are different from our institution's electrochemiluminescence immunoassay (ECLIA). Thus, these recommendations are a major departure from our current practice and could hardly be achieved in our local setting because our local TSH trimester-specific reference interval is not applicable due to a different assay used and the anti-TPO result is not readily available.

In this population-based study, we aimed to determine the maternal and perinatal outcomes of levothyroxine treatment in pregnant women, irrespective of antibody status, using both TSH cut points of 2.5 and 4.0 mIU/L according to the 2011 and 2017 ATA guidelines, respectively. These will be compared with the outcomes in untreated euthyroid pregnant women to support our current practice that levothyroxine treatment in subclinical hypothyroidism at a TSH cut-off of 2.5 mIU/L would show no maternal and perinatal harmful effects.

The general objective is to determine and compare the maternal and perinatal outcomes of pregnant women who are euthyroid (TSH 0.3-2.4 mIU/L) versus those with subclinical hypothyroidism (TSH 2.5-4.0 mIU/L, TSH > 4.0-10.0 mIU/L) treated with levothyroxine at Chong Hua Hospital from September 2017 to September 2018.More specifically:

1. To determine the prevalence of subclinical hypothyroidism (TSH ≥ 2.5 mIU/L) at Chong Hua Hospital from September 2017 to September 2018.
2. To determine and compare the clinical characteristics of pregnant patients who are euthyroid (TSH 0.3-2.4 mIU/L) versus those with subclinical hypothyroidism (TSH 2.5-4.0 mIU/L; > 4.0-10.0 mIU/L) as to:
   a. Age
   b. Parity
   c. Gestational age at first consult
4. To determine and compare the maternal and perinatal outcomes of pregnancy among patients who are euthyroid (TSH 0.3-2.4 mIU/L) versus those with subclinical hypothyroidism (TSH 2.5-4.0 mIU/L; > 4.0-10.0 mIU/L) treated with levothyroxine, as to:
   a. Mode of delivery: spontaneous vaginal delivery (SVD), cesarean section (CS), vacuum extraction
   b. Maturity of pregnancy: term, preterm, post-term
   c. Gestational diabetes mellitus (GDM)
   d. Gestational hypertension (HPN)
   e. Preeclampsia
   f. Premature rupture of membranes (PROM)
   g. Mean APGAR (appearance, pulse, grimace, activity, respiration) score at five minutes
   h. Birthweight: appropriate (AGA), small (SGA) and large (LGA) for gestational age
   i. Fetal distress
5. To determine the relative risk of levothyroxine treatment in pregnant women with TSH 2.5-4.0 mIU/L versus the untreated patients with TSH 0.3-2.4 mIU/L.
6. To determine the relative risk of levothyroxine treatment in pregnant women with TSH > 4.0-10.0 mIU/L versus the untreated patients with TSH 0.3-2.4 mIU/L.

Methods

This is a single-center, prospective cohort study conducted in the obstetric charity services of Chong Hua Hospital, a 660-bed capacity, tertiary hospital in Cebu City. The study protocol was approved by the hospital's institutional review board.

Subclinical hypothyroidism was defined in this study as a TSH concentration of 2.5-10.0 mIU/L regardless of FT4 levels. Patients with a TSH of 0.3-2.4 mIU/L were considered euthyroid and were not treated. The cohort was then divided into three groups depending on the baseline level of TSH: the euthyroid group with TSH 0.3-2.4 mIU/L serving as control subjects; those with subclinical hypothyroidism further subdivided into TSH level 2.5-4.0 mIU/L and TSH level >4.0-10.0 mIU/L. This was to validate our current practice of treating pregnant patients with levothyroxine at a TSH cut-off of 2.5 mIU/L and compare the pregnancy outcome with the euthyroid group and those with TSH >4.0-10 mIU/L.

Between September 2017 to September 2018, where 808 new antenatal patients were considered, the pregnancy

outcome in pregnant women who were found to have elevated TSH (≥2.5 mIU/L) irrespective of gestational age were compared with pregnant women with normal TSH (0.3-2.4 mIU/L).

Pregnant women with the following conditions were excluded: overt thyroid disorder, previous or present use of thyroxine or anti-thyroid drugs, multifetal gestation, known chronic disorders and those who had previous bad obstetric history with known cause.

At the time of orientation of the newly enroled pregnant women at the out-patient department (OPD) obstetric charity service, written informed consent was obtained and iinformation about demographic and clinical characteristics were collected on routine history taking and physical examination. Measurement of serum TSH by ECLIA was performed at the first antenatal examination in the same hospital laboratory. Other routine laboratory investigations were also performed such as pelvic ultrasound, CBC, OGTT, urinalysis, and tests to rule out HIV, HBV and syphilis.

All those with a baseline TSH ≥2.5 mIU/L were initially treated with levothyroxine 50 ug daily with appropriate adjustment of dosage to keep the TSH levels between 0.3-2.4 mIU/L. The study participants received standard prenatal care and were followed through to delivery with TSH monitoring every four to eight weeks.

The following maternal outcomes were diagnosed based on individual guidelines and documented. A delivery occurring before 37 completed weeks of gestation was considered preterm; beyond 42 weeks was considered post-term. Gestational diabetes mellitus (GDM) was diagnosed if one or more of these readings were elevated in the 75g oral glucose tolerance test: plasma glucose level at fasting ≥92 mg/dL, at one hour ≥180 mg/dL, and at two hours ≥153 mg/dL. Gestational hypertension (HPN) was defined as BP ≥140/90 mmHg after 20 weeks of gestation, with no previous history of hypertension, including preeclampsia and eclampsia. Preeclampsia was defined as persistent elevated blood pressure (≥140/90 mmHg) with proteinuria. Premature rupture of membranes (PROM) was defined as the rupture of the amniotic sac and chorionic membrane prior to the onset of labor.[11]

The following perinatal outcomes were assessed and documented. APGAR score as early assessment of a newborn with parameters (heart rate, respirations, muscle tone and movement, skin color/oxygenation, reflex irritability to tactile stimulation) checked five minutes after birth. Small for gestational age (SGA) neonates have a weight below the 10th percentile for the gestational age; large for gestational age (LGA) neonates have a weight >90th percentile for gestational age. Fetal distress was defined as fetal heart rate <120 bpm or >160 bpm, presence of meconium, signs of abnormal fetal movement. The documentation of fetal distress was based on the presence of fetal distress signs before or during labor and associated complications.[11]

All data were expressed as means +/ standard deviations or numbers and percentages. Statistical analysis was performed using the SPSS 16.0 software. F-test was used to compare continuous variables (maternal age, gestational age at delivery, TSH) and the chi-square test was used to compare categorical measures (maternal and perinatal outcomes). Results were also reported as relative risk with 95% confidence intervals (CIs), with untreated pregnant women as the reference group. *P*</0.05 was considered to be statistically significant.

Results

There were 808 pregnant women who reported to the obstetric charity service of Chong Hua Hospital from September 2017 to September 2018. Of these, 505 (62.5%) pregnant women were included in the analysis after applying the exclusion criteria.

Among these pregnant women, 404 were found euthyroid (TSH 0.3-2.4 mIU/L). A total of 101 (12.5%) women with subclinical hypothyroidism were identified and treated with levothyroxine, further subdivided based on baseline serum TSH levels: 81 women (80.2%) had serum TSH 2.5-4.0 mIU/L and 20 women (19.8%) had serum TSH > 4.0-10.0 mIU/L. This study has reported a 12.5% prevalence of maternal sublinical hypothyroidism in this cohort of patients.

The baseline characteristics of pregnant women who were included in the study is shown in Table I. Patients with TSH 2.5-4.0 mIU/L had older mean maternal age among the three groups (*p*=0.011). Most patients were nulliparous with no statistical difference among the three groups. There was a statistically significant difference (*p*=0.046) in the

Table I. A comparison of the clinical characteristics of pregnant patients who are euthyroid (TSH 0.3-2.5 mIU/L) versus those with subclinical hypothyroidism (TSH 2.5-4.0 and TSH > 4.0-10.0 mIU/L)

	TSH 0.3-2.4 (n=404)	TSH 2.5-4.0 (n=81)	TSH > 4.0-10 (n=20)	*p*-value
Mean age in years (SD)	28.6 (5.5)	30.5 (4.9)	29.6 (5.1)	0.011
Nulliparous (%)	228 (56.4)	45 (55.6)	13 (65.0)	0.738
Multiparous (%)	176 (43.6)	36 (44.4)	7 (35.0)	0.738
Gestational age at first consult (%)				
1st trimester (1-12 weeks)	303 (75)	50 (61.7)	13 (65.0)	0.046
2nd trimester (13-26 weeks)	81(20)	21 (25.9)	6 (30.0)	
3rd trimester (27-37 weeks)	20 (5)	10 (12.3)	1 (5.0)	

gestational age at first consult. Most euthyroid patients (75%) sought consult during the first trimester, while patients with maternal hypothyroidism presented at a later trimester - six (30%) patients with TSH >4.0-10.0 mIU/L during the second trimester while 10 (12.3%) patients with serum TSH 2.5-4.0 during the third trimester.

The maternal and perinatal outcomes of pregnancy in patients who are euthyroid compared to those with subclinical hypothyroidism treated with levothyroxine are shown in Table II.

A normal spontaneous vaginal delivery occurred mostly in euthyroid patients (80.7%). More patients (30%) with TSH >4.0-10.0 mIU/L delivered via caesarean section (30%) and vacuum extraction (5.0%) compared to the other two groups.

The three groups were not different with regard to documented complications of pregnancy, such as gestational diabetes, gestational hypertension, pre-eclampsia and premature rupture of membranes. However, an interesting finding in this study was that two patients (10%) with serum TSH >4.0-10.0 mIU/L had an increased rate of preterm delivery; those with TSH 2.5-4.0 mIU/L also had preterm delivery in six patients (7.41%) and two patients (2.47%) had post-term delivery compared with the euthyroid group. This occurred even after correction of thyroid function with levothyroxine (p=0.010).

There was no statistically significant association with the mean APGAR score at five minutes among the three groups. However, another interesting finding in this study is the delivery of seven (8.6%) SGA and two (2.5%) LGA infants in patients with baseline TSH 2.5-4.0 mIU/L even with levothyroxine treatment. On the other hand, 95% of those with baseline TSH >4.0-10.0 mIU/L had AGA infants.

A secondary analysis was made with adjustment for age and parity at enrolment. As shown in Table III, pregnant women treated with levothyroxine at baseline TSH 2.5-4.0 mIU/L showed no difference versus the untreated women with TSH <2.5 mIU/L in the maternal and perinatal outcomes measured.

Another comparison was made between pregnant women treated with levothyroxine at a baseline TSH >4.0-10.0 mIU/L versus untreated women with TSH <2.5 mIU/L. As shown in Table IV, there was no statistically significant difference between the two groups.

Table II. A comparison of the maternal and perinatal outcomes in pregnant patients who are euthyroid (TSH 0.3-2.4 mIU/L) versus those with subclinical hypothyroidism (TSH 2.5-4.0 mIU/L and TSH > 4.0-10.0 mIU/L) treated with levothyroxine

	TSH <2.5 (n=404)	TSH 2.5-4.0 (n=81)	TSH >4.0-10.0 (n=20)	*p*-value
Mode of delivery (%)				0.470
SVD	326 (80.7)	64 (79.0)	13 (65.0)	
CS	70 (17.3)	16 (19.8)	6 (30.0)	
Vacuum	8 (2.0)	1 (1.2)	1 (5.0)	
Maturity (%)				0.010
Term	399 (98.8)	73 (90.1)	18 (90.0)	
Pre-term	4 (0.99)	6 (7.41)	2 (10.0)	
Post-term	1 (0.25)	2 (2.47)	0	
GDM (%)	39 (9.7)	7 (8.6)	0	0.338
Gestational HPN (%)	8 (2.0)	0	0	0.362
Pre-eclampsia (%)	5 (1.2)	2 (2.5)	1 (5.0)	0.330
PROM (%)	2 (0.5)	0	0	0.780
Mean APGAR Score at 5 minutes (SD)	8.96 (0.30)	8.97 (0.16)	8.90 (0.31)	0.559
Birthweight (%)				0.026
AGA	376 (93.1)	72 (88.9)	19 (95.0)	
SGA	28 (6.9)	7 (8.6)	1 (5.0)	
LGA	0	2 (2.5)	0	
Fetal distress	29 (7.2)	5 (6.2)	3 (15)	0.386

Table III. A comparison of the outcome of levothyroxine treatment in pregnant women with baseline TSH 2.5-4.0 mIU/L versus untreated euthyroid women with TSH < 2.5 mIU/L.

Covariates	Unadjusted RR	Adjusted RR*	95% CI for Adjusted RR	*p*-value
Mode of delivery	1.221	1.071	0.586 - 1.960	0.823
Maturity	0.450	0.560	0.252 - 1.242	0.154
GDM	0.844	0.702	0.295 - 1.670	0.423
Pre-eclampsia	1.932	1.425	0.268 - 7.583	0.678
Mean APGAR score at 5 mins	1.309	1.519	0.472 - 4.890	0.484
Birthweight	0.686	0.848	0.366 - 1.966	0.700
Fetal distress	1.025	0.840	0.332 - 2.130	0.714

**Adjusted for age and parity*

***Gestational HPN and PROM are not included in covariates due to absence of case.*

Table IV. A comparison of the outcome of levothyroxine treatment in pregnant women with baseline TSH > 4.0-10.0 mIU/L versus untreated euthyroid women with TSH < 2.5 mIU/L

Covariates	Unadjusted RR	Adjusted RR*	95% CI for Adjusted RR	*p*-value
Mode of delivery	2.062	1.804	0.664 - 4.903	0.248
Maturity	1.156	1.304	0.165 - 10.316	0.802
Pre-eclampsia	4.168	3.074	0.337 - 28.076	0.320
Mean APGAR score at 5 mins	0.670	0.745	0.288 - 1.932	0.545
Birthweight	1.372	1.585	0.201 - 12.473	0.662
Fetal distress	2.351	1.865	0.507 - 6.860	0.348

**Adjusted for age and parity*

***Gestational HPN, GDM, PROM are not included in covariates due to absence of case.*

Discussion

This study reported a 12.5% prevalence of maternal sublinical hypothyroidism in this cohort of patients. This is comparable to a few reports from India which was as high as 13.5%.[12] Given the relatively high incidence of subclinical hypothyroidism, this showed the importance of routine thyroid screening in our setting.

While a number of studies of followed pregnant patients suffering from maternal hypothyroidism to determine adverse maternal and perinatal outcomes, at the time this study was conducted, there was limited data examining the possible effects of levothyroxine treatment in these patients. This study was therefore different to most previously reported studies that looked for an association between maternal hypothyroidism and adverse outcomes of pregnancy.

The baseline characteristics of pregnant women who were included in the study is shown in Table I. Patients with TSH 2.5-4.0 mIU/L had older mean maternal age among the three groups (p=0.011), although a difference of two years compared to the other groups may not be clinically important in these patients. There was a statistically significant difference (p=0.046) in the gestational age at first consult. This could mean that some patients with subclinical hypothyroidism may have missed the treatment opportunity at an earlier age of gestation.

The maternal and perinatal outcomes of pregnancy in patients who are euthyroid compared to those with subclinical hypothyroidism treated with levothyroxine are shown in Table II. An interesting finding in this study was that two patients (10%) with serum TSH >4.0-10.0 mIU/L had an increased rate of preterm delivery; those with TSH 2.5-4.0 mIU/L also had preterm delivery in six patients (7.41%) and two patients (2.47%) had post-term delivery compared with the euthyroid group. This occurred even after correction of thyroid function with levothyroxine (p=0.010). This may indicate that even with levothyroxine treatment, subclinical hypothyroidism during pregnancy could affect maturity of birth.

This is in contrast to one trial that evaluated the TSH cut-off of ≥ 4.0 mIU/L versus <4.0 mIU/L in a post hoc analysis. Among women with a TSH ≥4.0 mIU/L, there was a lower proportion of preterm delivery in the levothyroxine treated group compared with the untreated group (7.3% versus 19%, respectively; p-value not reported). Whereas in women with a TSH <4.0 mIU/L, there was higher preterm delivery rate compared with the untreated group (12.8% versus 8.3%, respectively; p-value not reported).[4]

Another interesting finding in this study is the delivery of seven (8.6%) SGA and two (2.5%) LGA infants in patients with baseline TSH 2.5-4.0 mIU/L even with levothyroxine treatment. On the other hand, 95% of those with baseline TSH >4.0-10.0 mIU/L had AGA infants. This could indicate that levothyroxine treatment may be beneficial to those with baseline TSH >4.0-10.0 mIU/L in terms of birth weight, but not in those with baseline TSH 2.5-4.0 mIU/L.

The prevalence of SGA in pregnant women with subclinical hypothyroidism has been well documented in several studies, but in only a few has the subclinical hypothyroidism been treated at initial presentation. In a recently published study by Maraka et al. from the Mayo Clinic, they reported a retrospective study of treated versus untreated hypothyroid control group and showed that SGA was significantly decreased in the levothyroxine treatment group (1.3% versus 10%; <0.001).[13]

In this study, in spite of the fact that patients were treated with levothyroxine at presentation and maintained the serum TSH at < 2.5mIU/L throughout pregnancy, the rate of SGA was 8.6% and LGA was 2.5%, raising the possibility that other factors may contribute to these adverse outcomes.

However, this needs to be considered in proper perspective, as the number of women delivering babies with SGA (n=7) and LGA (n=2) in our study was small. If there is a direct cause and effect relationship between women suffering subclinical hypothyroidism and subsequently delivering SGA or LGA infants, one of the factors may be the mean maternal age and the timing of testing and initiation of levothyroxine therapy.

A secondary analysis was made with adjustment for age and parity at enrolment. As shown in Table III and Table IV, pregnant women treated with levothyroxine at baseline TSH 2.5-4.0 mIU/L and TSH >4.0-10.0 showed no difference versus the untreated women with TSH <2.5 mIU/L in the maternal and perinatal outcomes measured.

In a study by Nazapour and colleagues, there was no significant difference in preterm delivery using the TSH cut-off of 2.5 mIU/L (RR 0.86; 95% CI: 0.47 to 1.55; *P*=0.61). However, log-binomial model analysis based on a cut point of 4.0 mIU/L demonstrated a significantly lower rate of preterm delivery in levothyroxine-treated women compared with those who received no treatment (RR: 0.38; 95% CI: 0.15 to 0.98; *P*=0.04).[14]

The findings of this study support the view that levothyroxine treatment in pregnant women with subclinical hypothyroidism at a TSH cut-off of 2.5 mIU/L shows no harmful effects. Nevertheless, without a matched untreated control group, we cannot conclude that all pregnant women with TSH ≥2.5 mIU/L should be treated with levothyroxine. Further investigation of the effects of thyroid function screening and prospective medical intervention on pregnant patients with subclinical hypothyroidism in a randomized, placebo-controlled experiment could verify these associations with adverse maternal and perinatal outcomes.

Limitations of the study

This study has some limitations. First, there was no matched untreated control group of pregnant women with subclinical hypothyroidism. Being a prospective cohort study, withholding treatment for a group of patients would be inappropriate and this study would not have gained IRB approval. However, the control group was the euthyroid pregnant women who do not warrant levothyroxine treatment. Second, the result of this study is applicable to patients with TSH values using the ECLIA method that is being utilized at Chong Hua Hospital. Third, FT4 values were not considered in the analysis because they are not considered in the treatment decision as well as in the adjustment of levothyroxine therapy. Fourth, the impacts of anti-thyroid antibodies were not taken into account in the assessment of maternal and perinatal outcomes because of its cost and unavailability. Fifth, the data was based from the practice of a single center and the sample size of pregnant women with subclinical hypothyroidism was small.

Conclusion

This study has shown a 12.5% prevalence of subclinical hypothyroidism in our setting. In the secondary analysis of this study adjusted for age and parity, there was no difference in the maternal and perinatal outcomes of pregnant patients who are euthyroid versus those with subclinical hypothyroidism treated with levothyroxine at a TSH threshold of 2.5-4.0 mIU/L and > 4.0-10.0 mIU/L. These findings support the view that levothyroxine treatment in pregnant women with subclinical hypothyroidism at a TSH cut-off of 2.5 mIU/L shows no harmful effects. Thus, the results of this study support the clinical practice in our institution of treating pregnant women with subclinical hypothyroidism at a TSH cut-off of 2.5 mIU/L.

References

1. **Abalovich M, Gutierrex S, Alcaraz G;** Overt and Subclinical Hypothyroidism Complicating Pregnancy. Thyroid, 12:63-8, 2002.
2. **Lazarus JH;** Screening for Thyroid Dysfunction in Pregnancy: Is it Worthwhile? J Thyroid Res, 3:97-112, 2011.
3. **Garber JR, Cobin RH, Gharib H, et al;** Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract, 18(6):988-1028, 2012.
4. **Negro R, Stagnaro-Green A;** Diagnosis and Management of Subclinical Hypothyroidism in Pregnancy. BMJ, 349:g4929, 2014.
5. **Chan S, Boelaert K;** Optimal Management of Hypothyroidism, Hypothyroxinemia and Euthyroid TPO Antibody Positivity Preconception and in Pregnancy. Clin Endocrinol, 82(3):313-26, 2015.
6. **Sheehan PM, Nankervis A, Araujo JE, et al;** Maternal Thyroid Disease and Preterm Birth: Systematic Review and Meta-analysis. J Clin Endocrinol Metab, 100:4325-31, 2015.
7. **Maraka S, Ospina NMS, O'Keeffe DT, et al;** Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-analysis. Thyroid, 26:580-90, 2016.
8. **Yamamoto JM, Benham JL, Nerenberg KA, et al;** Impact of Levothyroxine Therapy on Obstetric, Neonatal and Childhood Outcomes in Women with Subclinical Hypothyroidism Diagnosed in Pregnancy: A Systematic Review and Meta-analysis of Randomized Controlled Trials. BMJ Open, 8:e022837, July 2018.
9. **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, 27:315–89, 2017.
10. **Patal PC, Hamin J, Bautista A, et al**; Trimester-Specific Reference Interval for Thyroid Function Tests in Pregnant Filipino Women. JAFES, 31(1):19, April 2016.
11. **Chen LM, Du WJ, Dai Jie, et al;** Effects of Subclinical Hypothyroidism on Maternal and Perinatal Outcomes During Pregnancy: A Single-Center Cohort Study of a Chinese Population. Plos One, 9(10):2-3, October 2014.
12. **Sannaboraiah A, Upadhyaya R, Garag S, et al;** Subclinical Hypothyroidism in Pregnancy and Outcomes. Int J Reprod Contracept Obstet Gynecol, 6(4):1215-1216, April 2017.
13. **Maraka S, Ospina NMS, O'Keeffe DT, et al;** Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women with Subclinical Hypothyroidism. Thyroid, 26(7):980-986, November 2016.
14. **Nazapour S, Ramezani TF, Simbar M, et al;** Effects of Levothyroxine on Pregnant Women with Subclinical Hypothyroidism, Negative for Thyroid Peroxidase Antibodies. J Clin Endocrinol Metab, 1;103(3):926-935, March 2018.