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RESEARCH ARTICLE

THE EFFECT OF LEVOTHYROXINE TREATMENT ON MATERNAL AND PERINATAL OUTCOMES IN PREGNANT WOMEN WITH SUBCLINICAL HYPOTHYROIDISM: A 5-YEAR RETROSPECTIVE STUDY AT A TERTIARY CARE HOSPITAL IN TURKEY

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ABSTRACT

Subclinical hypothyroidism is characterized by elevated thyroid stimulating hormone (TSH) levels with normal free thyroxine (fT4) levels. The aim of this study was to compare obstetric and neonatal outcomes in pregnant women with and without treatment for subclinical hypothyroidism. In this study, maternal and perinatal outcomes were evaluated in a total of 270 pregnant women who were diagnosed with subclinical hypothyroidism as a result of screening performed in three trimesters of pregnancy between 2015 and 2020 and followed up in our clinic, 149 of whom received levothyroxine treatment and 121 of whom did not receive treatment. Further, different cutoff values for TSH were compared. The rates of neonatal intensive care unit (NICU) requirement were not different according to the levothyroxine use status of the patients (p=0.73, p>0.05). Miscarriage rates did not differ according to levothyroxine use (p=0,87, p>0,05). TSH, T4 and antithyroid peroxidase levels did not differ according to the maternal use of levothyroxine (p>0,05). Birth weight, gestational week at birth, 1- and 5-minute APGAR scores, neonatal TSH and T4 levels did not differ according to the maternal use of levothyroxine (p>0,05). Among the adverse maternal and perinatal outcomes, the need for NICU admission and the rates of placental abruption, fetal distress, preterm premature rupture of membranes, preeclampsia, preterm labor, and small for gestational age were not significantly different among the TSH cutoff groups (p>0,05). The rate of premature rupture of membranes was higher in the group with TSH levels ≥2.5 mIU/L (p=0.04). Choosing 2.5 mIU/L as the cutoff value for TSH levels allows early diagnosis of subclinical hypothyroidism with a higher rate in pregnant Turkish women and proactive therapeutic management. Our study provides limited evidence for the success of levothyroxine therapy for adverse obstetric and neonatal outcomes.

Keywords: *Adverse pregnancy-fetal outcomes, Levothyroxine, Pregnancy, Screening, Subclinical hypothyroidism, Thyroid hormone replacement.*

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1. INTRODUCTION

Thyroid diseases are recognized as the second most common endocrinopathies after gestational diabetes mellitus in women of reproductive age. Role of the thyroid hormone is crucial for a healthy pregnancy and fetal development. Maternal thyroid dysfunction may cause various adverse obstetric outcomes, including miscarriage, intrauterine growth restriction, hypertensive disorders, and preterm delivery [1]. Notably, fetal development of the thyroid tissue depends on uteroplacental levels of thyroid hormone. The incidence of subclinical hypothyroidism has been reported to be 2%–3% in pregnant women. Moreover, subclinical hypothyroidism is characterized by high thyroid-stimulating hormone (TSH) levels (2.5–10 mIU/L) and normal free thyroxine (fT4) levels in asymptomatic pregnant women. The fetus is particularly dependent on the mother's thyroid hormone during the first trimester. Thus, antibody tests are recommended for the treatment or follow-up of patients with subclinical hypothyroidism. Anti-TPO positivity can lead to negative consequences for the mother and fetus, and approximately 2-17% of women of reproductive age have anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) autoantibodies [2]. Further, the risk of thyroid dysfunction has been increasing in Turkey—an endemic region for iodine deficiency. There is no recommendation by the American College of Obstetricians and Gynecologists (ACOG) that the diagnosis and treatment of maternal subclinical hypothyroidism improves neurocognitive outcomes in children, and thyroid function tests are not recommended during pregnancy [3]. In contrast, the Turkish Society of Endocrinology and Metabolism (TSEM) advocates the initial measurement of TSH levels in all women planning pregnancy and in all pregnant women [4]. TSEM and American Thyroid Association (ATA) recommend that TSH levels should be 0.1–2.5, 0.2–3.0, and 0.3–3.0 mIU/L in the first and third trimester, respectively [2, 4]. Hormone replacement therapy for hypothyroidism involves the oral administration of T4 (levothyroxine). The American Endocrinology Society (ES) [5] and the European Thyroid Association [6] recommend starting this therapy in pregnant women with TSH levels >2.5 mIU/L and >3.0 mIU/L in the first trimester and in the second and third trimesters, respectively. If hypothyroidism is not treated in such cases, it may increase the risk of perinatal morbidity, preterm birth, miscarriage, low birth weight, and mortality [7]. Notably, thyroid screening is not recommended for cases other than pregnancy and infertility because the benefits of the therapy for subclinical hypothyroidism have not been clearly established [8-10]. However, managing subclinical hypothyroidism is important because it can progress to overt hypothyroidism and has negative effects on the cardiovascular system, fertility, quality of life, depression, and cognitive functions. Notably, TSH levels are elevated in 2%–5% of all pregnant women. Generally, TSH levels of >4 mIU/L are considered significant in pregnant women with subclinical hypothyroidism. In patients with TSH levels above the specified cutoff value, treatment planning is recommended if the anti-TPO level is also positive [2]. According to a study that used the cutoff value of 2.5 mIU/L for TSH levels, 25% of the population needed treatment for hypothyroidism; however, when the cutoff value was set at 4 mIU/L, there was a 10-fold decrease in the number of pregnant women receiving therapy [11]. The aim of this study was to compare obstetric and neonatal outcomes in pregnant women with subclinical hypothyroidism who received and did not receive treatment.

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2. MATERIALS AND METHODS

This retrospective cross-sectional case–control study was conducted between 2015 and 2020 at the Department of Obstetrics and Gynecology of Health Sciences University Umraniye Training and Research Hospital. Patients with maternal diseases, such as overt hypothyroidism, autoimmune thyroiditis, hyperthyroidism, thyroid cancer, congenital heart diseases, diabetes mellitus, antiphospholipid antibody syndrome, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, other autoimmune-related diseases, multiple pregnancies, and chronic hypertension were excluded from the study. Macrosomia, polyhydramnios, intrauterine fetal death, were excluded from the study. In contrast, a known history of hypothyroidism before pregnancy, levothyroxine users and nonusers and women with pregnancy-related complications, such as preeclampsia, oligohydramnios, SGA, LBW, gestational hypertension, gestational thrombocytopenia, cholestasis, PROM, PPROM, preterm labor, postterm pregnancy were included. A total of 439 pregnant women enrolled for the study; of these, 41 were excluded because they were diagnosed with overt hypothyroidism and autoimmune thyroiditis, and 128 were excluded because they were not followed up at our clinic and their deliveries were performed at an external facility. After implementing the inclusion and exclusion criteria, 270 pregnant women (149 receiving treatment and 121 not receiving treatment) were reviewed and included in the final analysis. The clinical and laboratuary data of all pregnant women from all three trimesters diagnosed with subclinical hypothyroidism were collected from the hospital automation system and retrospectively analyzed. Gravida, parity, number of abortions, gestational ages of all patients were recorded. Maternal serum TSH, T4 and anti-TPO levels were recorded. It was recorded whether they were diagnosed with hypothyroidism before pregnancy and whether they used levothyroxine. The gestational weeks when each patient gave birth, fetal weight, type of delivery, indications for cesarean section, gender of the newborns, appearance; pulse; grimace; activity; and respiration 1- and 5-minute (APGAR) scores, neonatal TSH and T4 values were also recorded. Those who received neonatal intensive care unit (NICU) support were determined. Obstetric anamnesis was taken from all pregnant women included in the study. Crown-rump length, last menstruation date were recorded. Preeclampsia, small for gestational age (SGA), low birth weight (LBW), preterm birth, preterm premature rupture of membranes (PPROM) were recorded. The diagnosis of preeclampsia was based on the guideline updated by ACOG in 2019 [12]. Fetal weight below the 10th percentile were termed as SGA. LBW was considered when it was below 2500 g. Births before 37 weeks of gestation were termed as premature births. Rupture of membranes before 37^{th} gestational week was designated as PPROM [13]. Pregnant women with gestational diabetes mellitus [14] who had a positive oral glucose tolerance test were excluded from the study, but pregnant women with placenta previa [15] were included. In our study, the normal ranges for TSH, T4, and anti-TPO levels were considered 0.1–2.5 mIU/L, 0.93–1.71 ng/dl, and <5.60 IU/mL, respectively. Based on the obtained results, TSH levels were classified into three groups: 2.5, 2.5–4, and 3–10 mIU/L. Different cutoff values for TSH levels were then compared between these groups. Subclinical hypothyroidism diagnosis of the patients included in the study was made according to the criteria by the ATA 2011, 2017 and ES 2012 [2, 5]. Previously, the upper limit for TSH value was specified as 2.5 mIU/L for the first trimester in the guidelines. In 2017, the upper limit was revised to 4 mIU/L. Therefore, in our study, both upper limits were used as cutoff values for comparison purposes. Ethical approval was obtained from the Health Sciences University Ümraniye

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Training and Research Hospital Ethics Committee (Date: April 14, 2020; confirmation number: B.10.1.TKH.4.34.H.GP.0.01/85). Informed consent was obtained from all the participants included in this cross-sectional retrospective study.

2.1. Statistical Analysis

Descriptive statistics were presented as mean, standard deviation (Avr±SD), confidence interval (95% CI) value for continuous variables. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Non-parametric methods were used because the measurement data in the study were not suitable for normal distribution (p=0.01) and the numbers within the group were not very high. Mann Whitney U test was used for pairwise comparisons and Kruskall Wallis test for triple comparisons. Chi-square test was used to evaluate the difference in group ratios. Fisher correction was applied if the expected cell value was less than 5%, 20% or more. $p<0.05$ was accepted as the critical value. The data were analyzed using the SPSS 25.0 (Statistical Packages of Social Sciences) program on the computer.

3. RESULTS

We found that the rate of NICU requirement was not different between levothyroxine users and nonusers (p=0.73, p>0.05). In contrast, the rate of diagnosis of hypothyroidism before pregnancy was different between levothyroxine users and nonusers, and the rate of levothyroxine use was higher in patients who were diagnosed with hypothyroidism before pregnancy (p=0.01, p<0.05). Notably, the mode of delivery (p=0.50, p>0.05) and infant gender (p=0.31, p>0.05) did not differ according to levothyroxine use. Taking maternal levothyroxine did not make a difference in all three trimesters (p=0.09, p>0.05) (Table 1a). Further, the age of the patients did not differ according to levothyroxine use (p=0.18, p>0.05). Gravida (p=0.02) and parity (p=0.01) were significantly higher among levothyroxine users than among nonusers. The rate of miscarriage did not significantly differ according to the maternal use of levothyroxine (p=0.87, p>0.05). Furthermore, TSH, T4, and anti-TPO levels did not differ according to levothyroxine use (p>0.05). Birth weight, gestational week at birth, 1- and 5-minute APGAR scores and neonatal TSH and T4 levels were not found to be different in those who received or did not receive levothyroxine (p>0.05) (Table 1b).

Table 1a: Examination of Patient Characteristics According to Levothyroxine Usage Status.

		Levothyroxine		**p**
		No (n=121) n (%)	Yes (n=149) n (%)	
NICU need	No Yes	101 (83.5) 20 (16.5)	122 (81.9) 27(18.1)	0.73
History of hypothyroidism	No Yes	75 (62) 46 (38)	68 (45.6) 81 (54.4)	0.01*
Delivery type	NSD C/S	60 (49.6) 61 (50.4)	80 (53.7) 69 (46.3)	0.50

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Gender	Female Male	48 (39.7) 73 (60.3)	68 (45.9) 80 (54.1)	0.31
Gestational ages	1st Trimester 2nd Trimester 3rd Trimester	98 (81) 19 (15.7) 4 (3.3)	133 (89.3) 11 (7.4) 5 (3.4)	0.09

**Chi-square test was performed *Significant difference at 0.05 level

Table 1b: Analysis of Patient Measurements According to Levothyroxine Usage Status.

	Levothyroxine				
	No (n=121)		Yes (n=149)		**p**
	Avr±SD	95% CI	Avr±SD	95% CI	
Age	28.44±6.2	27.32±29.55	29.36±5.18	28.52-30.19	0.18
Gravida	2.30±1.56	2.02±2.58	2.71±1.47	2.47-2.95	0.02*
Parity	0.85±1.01	0.67±1.03	1.29±1.08	1.11-1.46	0.01*
Abortus	0.45±0.97	0.28±0.63	0.44±0.92	0.29-0.58	0.87
TSH (mIU/L)	4.4±5.91	3.33±5.46	4.95±4.16	4.28-5.63	0.36
fT4 (ng/dL)	1.56±7.01	0.3±2.82	2.55±14.28	0.24-4.86	0.48
Anti-TPO (IU/mL)	194.03±322.23	94.86±293.19	160.5±275.07	89.44-231.56	0.57
Gestational age at birth	38.28±2.28	37.87±38.69	38.27±2.3	37.9-38.64	0.96
Birth weight	3237.85±595.86	3130.6±3345.1	3197.92±577.34	3104.45-3291.39	0.57
APGAR 1	8.46±1.17	8.25±8.67	8.54±0.97	8.38-8.69	0.57
APGAR 5	9.63±1.09	9.43±9.82	9.69±0.7	9.58-9.8	0.58
Newborn TSH (mIU/L)	4.77±4.19	3.6±5.94	4.86±4.2	3.78-5.95	0.90
Newborn fT4 (ng/dL)	1.21±0.25	1.15±1.28	1.25±0.25	1.19-1.32	0.41

***Kruskall Wallis test ** Mann Whitney U test *Significant difference at 0.05 level

We found that the need for NICU did not differ according to trimesters ($p=0.14$, $p>0.05$). Moreover, the rate of levothyroxine use was not different according to trimesters ($p=0.10$, $p>0.05$). However, the rate of patients diagnosed with hypothyroidism before pregnancy was different among the first, second, and third trimesters, and this rate was the highest in the first trimester ($p=0.01$, $p<0.05$). The mode of delivery ($p=0.89$, $p>0.05$) and infant gender ($p=0.33$, $p>0.05$) did not differ among the trimesters (Table 2a). Moreover, age, gravida, parity, and miscarriage rates were not different among

the trimesters (p>0.05). We also found that TSH, T4, and anti-TPO levels were not significantly different among the trimesters (p>0.05). No difference were found in terms of birth weight, gestational week at birth, 1- and 5-minute APGAR scores, neonatal TSH and T4 levels in all three trimesters (p>0.05) (Table 2b).

Table 2a: Investigation of Patient Characteristics by Gestational Ages.

		Gestational Ages			
		1st Trimester (n=231) n (%)	2nd Trimester (n=30) n (%)	3rd Trimester (n=9) n (%)	**p**
NICU need	No	195 (84.4)	22 (73.3)	6 (66.7)	0.14
	Yes	36 (15.6)	8 (26.7)	3 (33.3)	
Levothyroxine	No	98 (42.4)	19 (63.3)	4 (44.4)	0.10
	Yes	133 (57.6)	11 (36.7)	5 (55.6)	
History of hypothyroidism	No	104 (45)	30 (100)	9 (100)	0.01*
	Yes	127 (55)	0 (0)	0(0)	
Delivery type	NSD	111 (48.1)	14 (46.7)	5 (55.6)	0.89
	C/S	120 (51.9)	16 (53.3)	4 (44.4)	
Gender	Female	101 (43.9)	13 (43.3)	2 (22.2)	0.33
	Male	129 (56.1)	17 (56.7)	7 (77.8)	

**Chi-square test was performed *Significant difference at 0.05 level

Table 2b: Examination of Patient Measurements According to Gestational Ages.

	Gestational Ages						
	1st Trimester (n=231)		2nd Trimester (n=30)		3rd Trimester (n=9)		**p**
	Avr±SD	95% CI	Avr±SD	95% CI	Avr±SD	95% CI	
Age	29.17±5.74	28.43-29.92	27.2±4.74	25.43-28.97	28.89±6.13	24.17-33.6	0.20
Gravida	2.57±1.58	2.37-2.78	2.27±1.17	1.83-2.7	2.22±1.2	1.3-3.15	0.49
Parity	1.09±1.08	0.95-1.23	1.17±1.02	0.79-1.55	0.89±1.17	-0.01-1.79	0.79
Abortus	0.49±1.00	0.36-0.62	0.13±0.43	-0.03-0.3	0.22±0.44	-0.12-0.56	0.11
TSH (mIU/L)	4.76±5.14	4.1-5.43	4.56±4.72	2.8-6.32	3.7±1.88	2.26-5.15	0.81
fT4 (ng/dL)	2.29±12.52	0.66-3.91	1.14±1.3	0.65-1.63	0.74±0.14	0.63-0.84	0.82
Anti-TPO (IU/mL)	188.29±311.65	121.47-255.11	110.9±180.39	14.78-207.02	-	-	0.54
Gestational age at birth	38.33±2.08	38.06-38.6	37.87±3.49	36.56-39.17	38.22±2.49	36.31-40.14	0.58

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Birth weight	3237.77±564.69	3164.56-3310.98	3031±724.15	2760.6-3301.4	3268.33±540.24	2853.07-3683.6	0.18
APGAR 1	8.55±0.9	8.44-8.67	8.17±1.86	7.47-8.86	8.33±1.32	7.32-9.35	0.15
APGAR 5	9.72±0.64	9.64-9.8	9.3±1.91	8.59-10.01	9.44±1.01	8.67-10.22	0.04
Newborn TSH (mIU/L)	4.89±4.34	4.03-5.75	4.8±2.53	2.15-7.45	3.44±1.93	1.05-5.83	0.75
Newborn fT4 (ng/dL)	1.23±0.24	1.18-1.28	1.35±0.25	1.11-1.58	1.17±0.31	0.67-1.67	0.41

**Kruskall Wallis test *Significant difference at the 0.05 level

The rates of previous cesarean section (p=0.54), fetal distress (FDS) (p=0.23), nonprogressive labor (p=0.67), cephalopelvic disproportion (CPD) (p=0.61), malpresentation (p=0.52), placenta previa (p=0.49), and placental abruption (p=0.44) did not significantly differ according to TSH cutoff levels (Table 3).

Table 3: Cesarean section indications according to different TSH cut-off values.

		TSH cut-off values			**p**
		2.5 (mIU/L) n (%)	2.5-4 (mIU/L) n (%)	4-10 (mIU/L) n (%)	
Previous cesarean section	No	54 (68.4)	55 (67.1)	69 (63.9)	0.54
	Yes	25 (31.6)	27 (32.9)	39 (36.1)	
Fetal distress	No	68 (86.1)	72 (87.8)	98 (90.7)	0.23
	Yes	11 (13.9)	10 (12.2)	10 (93.3)	
Progress failure	No	78 (98.7)	80 (97.6)	107 (99.1)	0.67
	Yes	1 (1.3)	2(2.4)	1 (0.9)	
Cephalopelvic disproportion	No	77 (97.5)	81 (98.8)	106 (98.1)	0.61
	Yes	2 (2.5)	1 (1.2)	2 (1.9)	
Malpresentation	No	76 (96.2)	80 (97.6)	103 (95.4)	0.52
	Yes	3 (3.8)	2 (2.4)	5 (4.6)	
Placenta previa	No	78 (98.7)	80 (97.6)	107 (99.1)	0.49
	Yes	1 (1.3)	2 (2.4)	1(0.9)	
Placental abruption	No	74 (93.7)	78 (95.1)	106 (98.1)	0.44
	Yes	5 (6.3)	4 (4.9)	2 (1.9)	

**Chi-square test was performed *Significant difference at the 0.05 level

The need for NICU (p=0.16) placental abruption (p=0.44), FDS (p=0.23), preeclampsia (p=0.58), PPROM (p=0.33), preterm labor (p=0.18), and SGA/LBW (p=0.19) did not significantly differ

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according to TSH cutoff levels. Notably, the rate of PROM was higher in the groups with a TSH level of ≥2.5 mIU/L (p=0.04, p<0.05) (Table 4).

Table 4: Adverse maternal and perinatal outcomes according to different TSH cut-off values.

		TSH cut-off values			**p**
		2.5 (mIU/L) n (%)	2.5-4 (mIU/L) n (%)	4-10 (mIU/L) n (%)	
NICU need	No	68 (86.1)	66 (80.5)	89 (81.7)	0.16
	Yes	11 (13.9)	16 (19.5)	20 (18.3)	
Placental abruption	No	74 (93.7)	78 (95.1)	106 (98.1)	0.44
	Yes	5 (6.3)	4 (4.9)	2 (1.9)	
Fetal distress	No	68 (86.1)	72 (87.8)	98 (90.7)	0.23
	Yes	11 (13.9)	10 (12.2)	10 (93.3)	
Preeclampsia	No	77(97.5)	80(97.6)	105(97.7)	0.58
	Yes	2(2.5)	2 (2.4)	3(2.8)	
PPROM	No	79 (100)	80 (97.6)	104 (96.3)	0.33
	Yes	0 (0)	2 (2.4)	4 (3.7)	
PROM	No	71 (89.9)	64 (78)	89 (8 2.4)	0.04*
	Yes	8 (10.1)	18 (22)	19 (17.6)	
Preterm birth	No	77 (97.5)	77 (93.9)	100 (92.6)	0.18
	Yes	2 (2.5)	5 (6.1)	8 (7.4)	
Low birthweight and small-for-gestational age	No	75 (94.9)	81 (98.8)	107 (99.1)	0.19
	Yes	4 (5.1)	1 (1.2)	1 (0.9)	

**Chi-square test was performed *Significant difference at the 0.05 level

4. DISCUSSION

There is still no clear information about the benefit of levothyroxine treatment in pregnant women with subclinical hypothyroidism. Furthermore, the results of the present study are insufficient to make any suggestions for reducing adverse pregnancy outcomes and achieving positive neurocognitive outcomes in children using this therapy. This study investigating the effect of levothyroxine treatment on maternal and perinatal outcomes in pregnant women with subclinical hypothyroidism is one of the first in Turkey. We evaluated the pregnancy outcomes of patients who were followed up and underwent labor at our clinic within the past 5 years and who did or did not receive levothyroxine therapy after the diagnosis of subclinical hypothyroidism.

Since retrospective studies have reported fetal losses and neurodevelopmental disorders in infants born to mothers with subclinical hypothyroidism, lowering TSH levels to reference ranges by administering levothyroxine therapy has become a common practice. There is no study reporting the positive effects of maternal treatment on neuropsychological development in babies of pregnant

women with subclinical hypothyroidism [16]. TSEM reported that levothyroxine therapy reduces obstetric risk in pregnant women with subclinical hypothyroidism who test positive for anti-TPO antibodies. However, the need for this therapy in pregnant women with subclinical hypothyroidism who test negative for these antibodies is controversial owing to conflicting data on obstetric risks [4]. According to ES 2012, this treatment is recommended for all pregnant women with elevated TSH levels, regardless of their antibody status [5].

The cutoff values for TSH are extremely important because decreasing the upper limit of normal for TSH from 5 to 2.5 mIU/L increases the prevalence of subclinical hypothyroidism from 4.6% to 20% [17]. Notably, women with subclinical hypothyroidism have increased risks of complications associated with pregnancy and childbirth. The rate of spontaneous abortion was 17% in women testing positive for anti-TG and anti-TPO antibodies and 8.4% in women testing negative for these antibodies [18]. A previous study evaluated the risks associated with delivery and reported that the incidence of subclinical hypothyroidism was 2.3% in 25,756 pregnant women, and the risk of placental abruption and preterm delivery was two times higher in such patients than in normal women [19]. In addition, it was found that there was an increased risk of miscarriage, low birth weight and growth retardation in pregnant women with undiagnosed and untreated subclinical hypothyroidism.

Some studies have reported varying results related to the benefits of administering levothyroxine therapy for subclinical hypothyroidism. Previous double-blind randomized studies have reported that this therapy improved psychometric evaluation parameters and hypothyroidism symptom scores in patients with a TSH level of >10 mIU/L; however, it did not lead to any changes in patients with subclinical hypothyroidism and TSH levels of <10 mIU/L [20, 21]. Among the poor maternal and perinatal outcomes evaluated in the present study, the need for NICU admission and the rates of placental abruption, FDS, PPROM, preeclampsia, preterm labor, and SGA/LBW did not significantly differ among the groups stratified according to different TSH cutoff levels. However, the rate of PROM was higher in groups with TSH levels of ≥2.5 mIU/L. The significance of administering levothyroxine therapy to pregnant women with a TSH level of ≥2.5 mIU/L has not been clearly established because it is not possible to predict which pregnant woman will develop PROM.

Regarding the indications for cesarean section according to different TSH cutoff groups, no significant difference was found in terms of previous cesarean section, FDS, nonprogressive labor, CPD, malpresentation, placenta previa, and placental abruption. Notably, our findings do not support the treatment of subclinical hypothyroidism diagnosed during pregnancy.

In a previous study, TSH levels did not increase in untreated pregnant women with subclinical hypothyroidism, but these levels were found to be high in mothers with positive anti-TPO antibody during pregnancy [22]. In our study, TSH, T4, and anti-TPO levels were not different between levothyroxine users and nonusers. Moreover, there was no difference between birth weight, gestational week at birth, 1- and 5-minute APGAR scores and neonatal TSH and T4 levels according to maternal levothyroxine use. In one of the previous studies, it was shown that the risk of miscarriage increased in anti-TPO positive pregnant women [16]. In a study conducted with pregnant women with subclinical hypothyroidism with a TSH level of 2.5-4 mIU/L, the rate of preterm birth was found to be

significantly higher, while fetal weight and gestational week at birth were found to be significantly lower [23]. In addition, in a study of pregnant women with subclinical hypothyroidism and positive anti-TPO antibody, levothyroxine therapy reduced the risk of preterm delivery and amniotic fluid abnormalities [24]. In another study involving the use of levothyroxine, the risks of miscarriage, gestational hypertension, intrauterine growth retardation, low birth weight, and preterm delivery were not significantly higher in women with subclinical hypothyroidism than in women with euthyroidism [25]. Moreover, it has been reported that the treatment of subclinical hypothyroidism with levothyroxine significantly reduces the incidence of preterm delivery, miscarriage, postpartum hemorrhage, and low birth weight [26]. In the present study, gravida and parity were significantly higher in levothyroxine users. However, no difference was found in the rate of miscarriage according to the maternal use of levothyroxine.

In a study of pregnant women at increased risk for cesarean section due to placental abruption, anemia, postpartum hemorrhage, and preterm delivery (3.13-fold increase when TSH level was >3 mIU/L at 16 weeks of gestation), maternal–fetal adverse reactions, such as low birth weight and impaired fetal brain development, were reported [16]. One study showed no statistically significant difference in obstetric and neonatal outcomes between the levothyroxine group and the control group [27]. Additionally, a previous study found no evidence on the benefit of levothyroxine therapy for pregnant women with subclinical hypothyroidism in terms of pregnancy, neonatal, and childhood outcomes [28]. Similarly, in our study, indications for cesarean section did not increase and there were no maternal or neonatal adverse outcomes, except for PROM.

A previous study suggested that levothyroxine improves pregnancy-related outcomes in patients with subclinical hypothyroidism as well as the neurointellectual development of newborns [29]. In contrast, we found no significant difference in NICU requirement, mode of delivery, gestational week at birth, mean age, and infant gender according to the maternal use of levothyroxine.

This study has some limitations. First, the prevalence of hypothyroidism was not determined. Second, the infant neurocognitive status was not assessed prospectively. Third, levothyroxine dose, race, ethnicity, iodine intake, body mass index before pregnancy, and socioeconomic status were not analyzed. Finally, we did not consider the factors influencing TSH levels and time of the day of blood collection during the diagnosis of subclinical hypothyroidism as this was a retrospective study.

This study also has pertinent strengths. First, to the best of our knowledge, this is the first study in Turkey evaluating maternal and perinatal outcomes and comparing patients receiving thyroid hormone replacement therapy with those not receiving the therapy. Second, in contrast to other studies, different cutoff values were evaluated in the present study.

5. CONCLUSION

Subclinical hypothyroidism is believed to cause pregnancy-related complications and adverse obstetric outcomes, such as placental insufficiency; however, there is a lack of solid evidence on this subject. We believe that future studies involving large patient groups in our country, which is an

endemic region for goiter, will provide a better understanding of the subject. In addition to the higher incidence of PROM in pregnant women with a TSH cutoff of ≥2.5 mIU/L, the benefit of thyroid hormone replacement therapy for other obstetric complications is questionable. This study did not provide conclusive evidence regarding the benefit of maternal levothyroxine therapy on maternal and fetal outcomes in pregnant women with subclinical hypothyroidism.

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