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# Comparison of fetal thyroid measurements between treated subclinical hypothyroidism and euthyroid pregnancies: A prospective observational study

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## MAIN POINTS

- Adequately treated maternal subclinical hypothyroidism does not significantly affect fetal thyroid dimensions, suggesting that appropriate levothyroxine therapy normalizes potential developmental impacts on fetal thyroid morphology.
- No significant correlations were found between maternal TSH levels, levothyroxine dosage, and fetal thyroid measurements, indicating that fetal thyroid development progresses independently when maternal thyroid function is appropriately managed.
- Amniotic fluid index remained significantly elevated in the subclinical hypothyroidism group despite treatment, revealing a potential subclinical manifestation of maternal thyroid dysfunction that persists even with adequate levothyroxine therapy.
- Standardized ultrasound measurement protocols with high reproducibility (ICC: 0.89, kappa: 0.85) demonstrated the feasibility of reliable fetal thyroid assessment during routine prenatal care.
- Early diagnosis and treatment of subclinical hypothyroidism are crucial for ensuring normal fetal thyroid development, supporting current guidelines for levothyroxine therapy in pregnancy.

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## ABSTRACT

**Aim:** To investigate the impact of maternal subclinical hypothyroidism (SCH) treated with levothyroxine on fetal thyroid dimensions during pregnancy.

**Materials and Methods:** In this prospective observational study, 50 pregnant women with treated SCH and 52 euthyroid controls underwent ultrasonographic evaluation between 20 and 39 gestational weeks were recruited. Fetal thyroid circumference (FTC) and fetal thyroid area (FTA) were measured, and correlations with maternal TSH levels and levothyroxine dosage were analyzed.

**Results:** No significant differences were found between the in fetal thyroid measurements in SCH and control groups before and after adjustment for gestational age. Correlation analyses revealed negligible associations between maternal thyroid function parameters and fetal thyroid size. Although the levothyroxine dose showed a weak negative trend with fetal thyroid measurements, the difference was not statistically significant. The amniotic fluid index (AFI) was significantly higher in the SCH group despite treatment.

**Conclusion:** Adequately treated maternal SCH does not appear to affect fetal thyroid development. These findings support the importance of early diagnosis and levothyroxine therapy for normalizing maternal thyroid function and potentially protecting fetal outcomes.

**Keywords:** Hypothyroidism, Pregnancy, Prenatal ultrasonography, Thyroxine

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## INTRODUCTION

Thyroid hormones (THs), primarily thyroxine (T4) and triiodothyronine (T3), are indispensable regulators of human development, metabolism, and homeostasis, beginning from the earliest stages of embryogenesis. They play crucial roles in cell differentiation, growth, neurogenesis, and energy metabolism, and are particularly essential for fetal brain development and thermoregulation [1]. The physiological demands of pregnancy induce significant alterations in thyroid hormone production, transport, and metabolism to accommodate maternal and fetal needs. These changes, in turn, increase the vulnerability of women to thyroid dysfunction during gestation.

Thyroid dysfunction, defined as excessive or insufficient pro-

duction of hormones by the thyroid gland, is one of the most common endocrine disorders affecting women of reproductive age, including during pregnancy [2]. Throughout the gestational period, a range of thyroid dysfunctions may occur, including overt hypothyroidism, subclinical hypothyroidism (SCH), and hyperthyroidism [3]. Overt hypothyroidism is defined as the presence of serum thyroid-stimulating hormone (TSH) levels greater than 10 mIU/L and decreased fT4 concentrations. SCH is characterized by elevated TSH levels, whereas fT4 concentrations are normal [4]. Epidemiological data indicate that SCH affects approximately 10% of the adult population and has a prevalence of 3.47% among pregnant women [5]. The major etiology of hypothyroidism is iodine deficiency in developing countries, whereas autoimmune thyroiditis is the primary factor in [6].

In 2011, the American Thyroid Association (ATA) published standardized guidelines for the management of thyroid dysfunction in pregnancy. This recommendation recommends upper limits of 2.5 mIU/L and 3.0 mIU/L for the first and second trimesters, respectively, for the diagnosis of subclinical hypothyroidism in pregnancy. Consequently, after thorough examination of population samples from many ethnic groups, the ATA updated these guidelines in 2017, establishing the maximum limit for normal blood TSH levels in early pregnancy at 4 mIU/L [7].

The fetal thyroid gland achieves functional maturity between 18 and 20 weeks of gestation, and during early pregnancy, the fetus predominantly relies on maternal circulating fT4 for growth and development [8]. Consequently, maternal fT4 serves as the sole supply of thyroid hormone for the developing fetus throughout this period. During early gestation, the fetus requires maternal THs for neuronal proliferation and migration [9]. Maternal thyroid hormone deficiency can result in various complications during pregnancy. Neurological deficits in infancy and adolescence, including reduced intelligence quotients, delays in neurocognitive functioning, and underdeveloped psychomotor skills, are major complications of maternal hypothyroidism in early gestation [10].

In addition to long-term neurodevelopmental risks, maternal hypothyroidism has also been linked to numerous obstetric complications. These include miscarriage, preterm birth, preeclampsia, placental abruption, gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), and increased perinatal mortality [11–13].

Despite the established association between maternal thyroid dysfunction and adverse outcomes, the precise mechanisms underlying these effects are still not fully understood. Several pathophysiological pathways have been proposed. The initial mechanism involves the direct influence of maternal T4 on the developing fetal neurological system through specific thyroid hormone receptors, which has been corroborated by animal studies identifying receptor pathways [14]. Another hypothesis suggests that alterations in maternal thyroid status may interfere with the maturation and regulatory capacity of the fetal hypothalamic-pituitary-thyroid (HPT) axis, which governs the fetal endocrine response. A less frequently explored but potentially significant mechanism proposed is that maternal thyroid dysfunction may directly influence the development and morphology of the fetal thyroid gland itself. This could occur via disruptions in maternal–fetal thyroid hormone transfer or through immunological and metabolic influences, potentially resulting in long-lasting structural or functional alterations.

The third hypothesis, which has received insufficient attention in the literature, proposes that maternal thyroid dysfunction may directly affect fetal thyroid tissue development, potentially leading to structural changes that persist postnatally. This hypothesis is particularly significant as it offers a quantifiable parameter through prenatal ultrasound measurement of fetal thyroid size, yet there remains a critical gap in research specifically examining the relationship between maternal SCH, levothyroxine treatment, and fetal thyroid dimensions. Understanding these mechanisms is crucial because they may represent different pathways through which maternal thyroid status ultimately influences fetal cognitive and physiological development.

In this study, we aimed to investigate the relationship between maternal thyroid function and fetal thyroid development by comparing fetal thyroid gland measurements obtained via ultrasonography in pregnant women diagnosed with and treated for SCH and those in euthyroid pregnant women. Through this comparison, we sought to provide insights into the mechanisms by which maternal thyroid status may influence fetal endocrine organogenesis and overall development, with potential implications for prenatal surveillance and therapeutic strategies.

## MATERIALS AND METHODS

### *Study design and setting*

This prospective observational study was performed in the Department of Perinatology, Haseki Training and Research Hospital, University of Health Sciences, Istanbul, Turkey, between January and December 2024. The study protocol received approval from the Institutional Ethics Committee (Registration Number: 23-2024 dated October 9, 2024) and was executed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants following the provision of detailed information regarding the study protocols.

### *Participants*

Initially, 140 pregnant women were assessed for eligibility. Among them, 38 were excluded due to chronic maternal conditions (n=5), fetal chromosomal abnormalities (n=5), incomplete laboratory data (n=18), and inadequate ultrasound imaging (n=10). As a result, 102 participants met the inclusion criteria and were enrolled in the study. The participants were subsequently divided into two groups: 50 preg-


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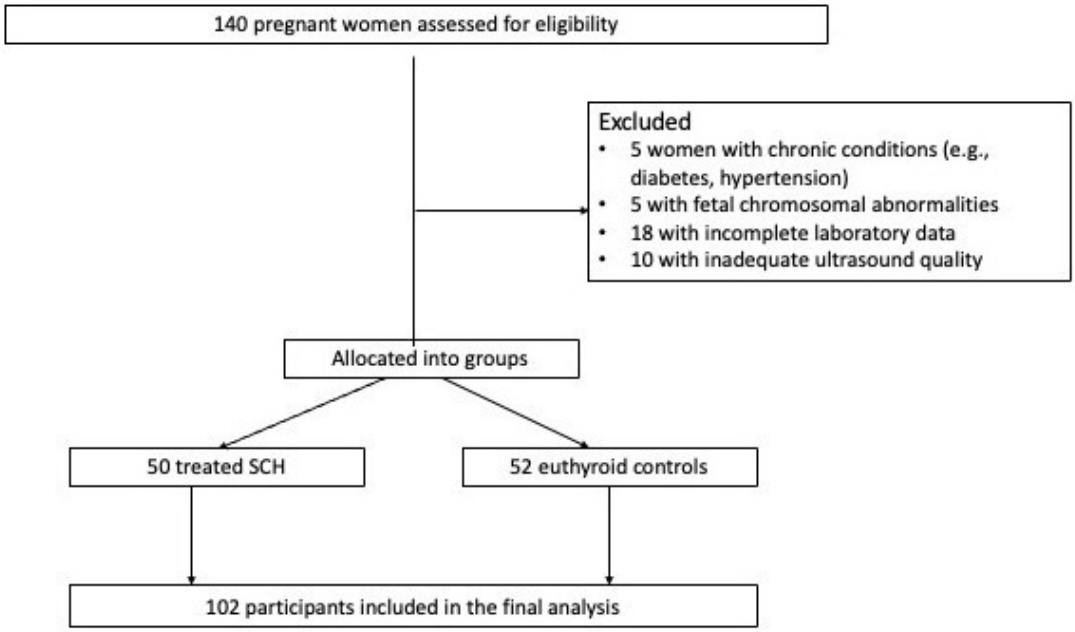


**Figure 1.** Flowchart of participant enrollment, exclusion, group allocation, and inclusion in final analysis.

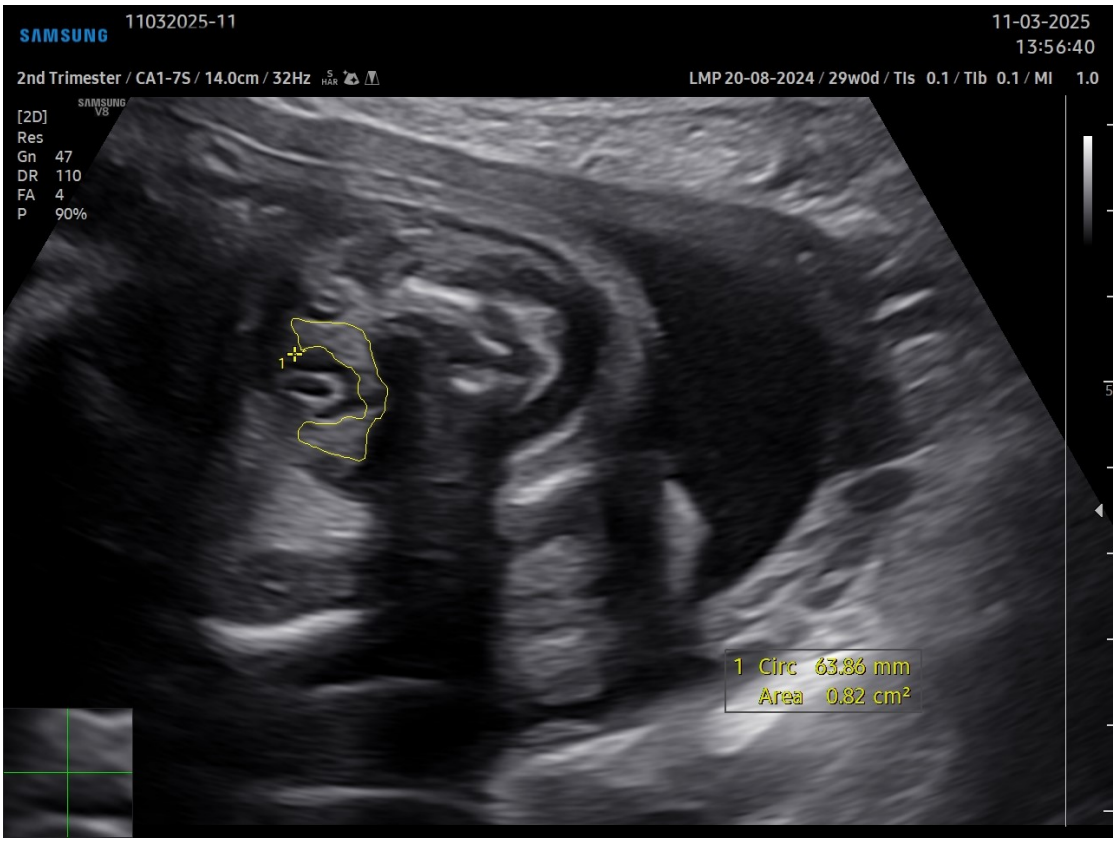


**Figure 2.** Axial view of the fetal neck showing thyroid gland measurement with circumference and area obtained using caliper and field measurement tools.

nant women with treated SCH and 52 euthyroid controls. The participant selection process and study flow are illustrated in Figure 1.

The study included patients diagnosed with SCH either before pregnancy or during the first trimester (defined by TSH levels exceeding 4 mIU/L with normal fT4 values; normal reference range for free T4 was 8.9–17.1 ng/L and for free T3 was 2.0–4.4 ng/L, measured by chemiluminescent immunoassay). Additionally, euthyroid pregnant women were included as a control group to enable a comparative analysis


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between those with treated SCH and those with normal thyroid function. Iodine intake was not systematically assessed or standardized among participants. Therefore, variations in iodine status constitute a potential confounding factor, and this limitation is acknowledged in the Discussion section. Gestational age was precisely established by confirming the last menstrual period on the first trimester CRL measurement.

The subsequent circumstances were excluded from the study: multiple gestations; pre-existing maternal conditions (including chronic hypertension, renal disease, hepatic disorders, other endocrine disorders); major neurological or psychiatric disorders; fetal structural or chromosomal abnormalities; known placental pathologies; cases with incomplete laboratory assessments or inadequate ultrasound examinations; and those who did not provide written informed consent. The sample size calculation was performed using G*Power software (release 3.1.9.7, from Heinrich Heine University in Düsseldorf, Germany). Drawing on earlier research that examined fetal measurements in pregnancies complicated by thyroid disorders, we selected a moderate effect size (d=0.6) for our comparative analysis between the two separate groups. With a type I error (α) of 0.05 and type II error (β) of 0.20 (corresponding to 80% power), the minimum required sample size was calculated as 45 participants per group. Considering potential dropouts and technical difficulties during ultrasound measurements, we aimed to include at least 50 participants in each group. The final study population comprised 102 participants (50 in the SCH group and 52 in the control group), exceeding the minimum requisite sample size.

### *Ultrasound imaging methods*

The fetal thyroid gland can be reliably assessed after 14 weeks by transvaginal ultrasonography and after 18 weeks by transabdominal ultrasonography [15]. Despite its clinical importance, few studies in the literature have established normative data on fetal thyroid size across gestational ages [16,17].

In our study, all ultrasonographic examinations were performed by a single experienced operator using a high-resolution ultrasound device (SAMSUNG V8, Samsung Medical Systems, Potenza, Italy) equipped with a convex array transducer (frequency range: 2–8 MHz).

A standardized imaging protocol was strictly followed to minimize interindividual variability in fetal thyroid measurements. Imaging was performed in the axial plane of the fetal neck at the level of the transverse view of the trachea, where the trachea appears centrally located between the two carotid arteries. Both lobes of the thyroid gland were identified based on their hyperechoic contours and homogeneous internal echotextures. The circumference of each lobe was manually traced using the ultrasound machine's caliper tool, and the area ($cm^2$) was calculated automatically using the integrated field measurement function (Figure 2). Special care was taken to avoid compression artifacts, and all measurements were obtained with the fetal neck in a neutral position (neither flexed nor extended) to prevent distortion. To ensure the reliability of the measurements, intraobserver reproducibility was evaluated by repeating measurements in 20 randomly selected fetuses after a 1-week interval by the same operator, yielding an intraclass correlation coefficient (ICC) of 0.89 (95% CI: 0.872–0.918). Interobserver reproducibility was assessed by a second independent sonographer who performed measurements on another 20 fetuses, resulting in a Cohen's kappa coefficient of 0.85, indicating excellent agreement.

### *Statistical analysis*

The distribution of continuous variables was assessed using both the Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables that exhibited a normal distribution were expressed as mean ± standard deviation (SD) and compared between groups using Student's t-test, whereas non-normally distributed variables were expressed as median (interquartile range, IQR) and compared using the Mann-Whitney U test. Correlation analyses were performed using Pearson's correlation coefficient for normally distributed variables and Spearman's correlation coefficient for nonnormally distributed variables. For categorical variables, statistical comparisons between groups were performed using appropriate tests based on the distribution of expected frequencies. Specifically, the Chi-square test was used when the expected frequencies met standard assumptions (expected count $\geq$5 in at least 80% of cells), and Fisher's exact test was applied when these assumptions were not satisfied. This approach ensured the validity of the statistical inferences for all the categorical data analyses. Statistical significance was defined as a p-value less than 0.05. To adjust for variations in gestational age, z-scores were calculated for fetal ultrasound measurements based on the entire study population (n=102), and group comparisons were made using Student's t-test. The correlation strength was classified as negligible ($|r| < 0.1$), weak ($0.1 \leq |r| < 0.3$), moderate ($0.3 \leq |r| < 0.5$), strong ($0.5 \leq |r| < 0.7$), or very strong ($|r| \geq 0.7$). For subgroup analyses, SCH patients were divided into low-dose ($\leq$50 mcg/day) and high-dose (>50 mcg/day) levothyroxine groups, and linear regression analyses were conducted to explore the relationship between levothyroxine dose and fetal thyroid dimensions, with coefficients of determination ($R^2$) reported.

## RESULTS

The study population comprised 102 pregnant women: 50 with treated SCH and 52 euthyroid controls. Table 1 shows the demographic and clinical attributes of pregnant women with SCH (n=50) compared to the control group (n=52). Maternal age was similar between groups (p=0.124), whereas women with SCH had significantly higher weight (77.02 ± 14.65 kg vs. 70.60 ± 13.29 kg, p=0.022). Obstetric history parameters exhibited no significant differences between the groups (p>0.05).


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**Table 1.** Demographic and clinical characteristics of pregnant women with and without SCH.

| Variable | SCH Group (n=50) | Control Group (n=52) | p-value |
|---|---|---|---|
| Maternal Characteristics | | | |
| Age (years) | 30.84 ± 6.11 | 29.12 ± 5.13 | 0.124 |
| Weight (kg) | 77.02 ± 14.65 | 70.60 ± 13.29 | 0.022* |
| Height (cm) | 160.44 ± 5.63 | 160.92 ± 5.31 | 0.655 |
| Gravidity | 3.00 (2.00-4.00) | 2.00 (3.00) | 0.083 |
| Parity | 1.34 ± 1.14 | 1.27 ± 1.12 | 0.752 |
| Abortion | 0.00 (1.00) | 0.00 (0.00) | 0.690 |
| Laboratory Values | | | |
| TSH (mIU/L) | 6.53 ± 1.88 | 2.07 ± 0.50 | <0.001* |
| T3 (ng/L) | 3.05 ± 0.52 | 3.02 ± 0.56 | 0.758 |
| T4 (ng/L) | 10.82 (3.40) | 10.73 (1.69) | 0.324 |
| Fetal Ultrasound Measurements | | | |
| Gestational Week | 24.00 (7.00) | 26.00 (7.00) | 0.098 |
| BPD (mm) | 60.96 ± 15.18 | 67.62 ± 11.90 | 0.015* |
| HC (mm) | 233.97 ± 52.16 | 248.86 ± 43.41 | 0.120 |
| AC (mm) | 216.09 ± 61.36 | 232.89 ± 51.91 | 0.139 |
| FL (mm) | 43.49 (18.97) | 47.14 (15.96) | 0.246 |
| EFW (g) | 1068.62 ± 877.88 | 1194.03 ± 717.16 | 0.429 |
| AFI | 55.16 ± 8.84 | 47.83 ± 10.86 | 0.001* |
| Fetal Thyroid Measurements | | | |
| FTC (cm) | 4.99 ± 1.74 | 5.12 ± 1.36 | 0.671 |
| FTA (cm²) | 0.75 ± 0.49 | 0.82 ± 0.42 | 0.427 |

*Statistically significant (p<0.05). Data with normal distribution are presented as mean ± standard deviation, while data with non-normal distribution are presented as median (IQR). The IQR (interquartile range) represents the difference between Q3 and Q1 as a single value.
SCH: Subclinical Hypothyroidism, TSH: Thyroid Stimulating Hormone, BPD: Biparietal Diameter, HC: Head Circumference, AC: Abdominal Circumference, FL: Femur Length, EFW: Estimated Fetal Weight, AFI: Amniotic Fluid Index, FTC: Fetal Thyroid Circumference, FTA: Fetal Thyroid Area.

**Table 2.** Z-score comparison of fetal ultrasound and thyroid measurements.

| Variable | SCH Group (n=50) | Control Group (n=52) | t-value | p-value |
|---|---|---|---|---|
| Fetal Biometry Z-scores | | | | |
| BPD (mm) | -0.15 ± 1.07 | 0.14 ± 0.84 | -1.58 | 0.118 |
| HC (mm) | -0.13 ± 1.09 | 0.12 ± 0.90 | -1.26 | 0.211 |
| AC (mm) | -0.14 ± 1.13 | 0.13 ± 0.85 | -1.40 | 0.165 |
| FL (mm) | -0.17 ± 0.92 | 0.16 ± 1.05 | -1.74 | 0.085 |
| EFW (g) | -0.08 ± 1.10 | 0.08 ± 0.90 | -0.83 | 0.409 |
| AFI | 0.34 ± 0.81 | -0.33 ± 1.00 | 3.73 | <0.001* |
| Fetal Thyroid Z-scores | | | | |
| FTC (cm) | -0.07 ± 1.14 | 0.07 ± 0.85 | -0.72 | 0.471 |
| FTA (cm²) | -0.08 ± 1.07 | 0.08 ± 0.93 | -0.81 | 0.419 |

*Statistically significant (p<0.05). BPD: Biparietal Diameter, HC: Head Circumference, AC: Abdominal Circumference, FL: Femur Length, EFW: Estimated Fetal Weight, AFI: Amniotic Fluid Index, FTC: Fetal Thyroid Circumference, FTA: Fetal Thyroid Area.

TSH levels were significantly elevated in the SCH group (6.53 ± 1.88 mIU/L vs. 2.07 ± 0.50 mIU/L, p<0.001), with T3 and T4 levels remaining similar between groups. Fetal ultrasound measurements showed significantly smaller BPD in fetuses of SCH mothers (p=0.015) and higher AFI in the SCH group (p=0.001). Other fetal biometric parameters and gestational age showed no significant differences between groups. Fetal thyroid circumference (FTC) and fetal thyroid area (FTA) were comparable between groups (p=0.671 and p=0.427, respectively).

To standardize and compare fetal ultrasound measurements between groups, we calculated Z-scores using the entire study population (n=102) as reference. Table 2 presents the z-score comparison of fetal ultrasound and thyroid measurements between the SCH and control groups. Upon adjustment for gestational age using z-scores, most fetal biometry measurements exhibited no statistically significant variations between the groups. The z-scores for fetal biometric measures showed no significant differences between the SCH and control groups (all p>0.05). The AFI z-score was considerably elevated in the SCH group (0.34 ± 0.81) relative to the control group (-0.33 ± 1.00, p<0.001). Fetal thyroid measurements expressed as z-


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**Table 3.** Correlation analysis between maternal tsh, levothyroxine dose and fetal thyroid measurements.

| Parameters | Coefficient | p-value | Strength | n |
|---|---|---|---|---|
| All Participants | | | | |
| TSH - FTC | -0.013 | 0.896 | Negligible | 102 |
| TSH - FTA | -0.027 | 0.788 | Negligible | 102 |
| Hypothyroidism Group | | | | |
| TSH - FTC | 0.062 | 0.668 | Negligible | 50 |
| TSH - FTA | 0.080 | 0.581 | Negligible | 50 |
| Levothyroxine dose - FTC | -0.156 | 0.279 | Weak | 50 |
| Levothyroxine dose - FTA | -0.207 | 0.149 | Weak | 50 |

TSH: Thyroid Stimulating Hormone, FTC: Fetal Thyroid Circumference, FTA: Fetal Thyroid Area. Correlation strength interpretation: $|r| < 0.1$: Negligible; $0.1 \leq |r| < 0.3$: Weak; $0.3 \leq |r| < 0.5$: Moderate; $0.5 \leq |r| < 0.7$: Strong; $|r| \geq 0.7$: Very strong.

**Table 4.** Comparison of fetal thyroid measurements by levothyroxine dose groups and regression analysis.

| Analysis | FTC (cm) | FTA (cm²) | p-value |
|---|---|---|---|
| Dose Group Comparison | | | |
| Low dose (≤50 mcg, n=32) | 5.190 ± 1.609 | 0.803 ± 0.455 | - |
| High dose (>50 mcg, n=18) | 5.104 ± 1.702 | 0.721 ± 0.502 | - |
| p-value | 0.855 | 0.557 | - |
| Linear Regression Analysis | | | |
| Regression equation | FTC = 5.570 - 0.007 × Dose | FTA = 0.910 - 0.002 × Dose | - |
| $R^2$ | 0.028 | 0.043 | - |
| p-value | 0.279 | 0.149 | - |

FTC: Fetal Thyroid Circumference; FTA: Fetal Thyroid Area; $R^2$: coefficient of determination.

scores also showed no significant differences between groups, with FTC z-scores of -0.07 ± 1.14 vs. 0.07 ± 0.85 (p=0.471) and FTA z-scores of -0.08 ± 1.07 vs. 0.08 ± 0.93 (p=0.419) for the SCH and control groups, respectively.

Correlation studies were conducted to investigate the associations among maternal TSH levels, levothyroxine dosage, and fetal thyroid measurements (Table 3). In the overall study population (n=102), no significant correlations were found between maternal TSH and FTC (r=-0.013, p=0.896) or FTA (r=-0.027, p=0.788), with both showing negligible correlation strength. Similarly, within the SCH group (n=50), maternal TSH levels showed negligible correlations with FTC (r=0.062, p=0.668) and FTA (r=0.080, p=0.581). The analysis of levothyroxine treatment dose in the SCH group revealed weak negative correlations with both FTC (r=-0.156, p=0.279) and FTA (r=-0.207, p=0.149), but these associations did not reach statistical significance.

To evaluate the potential effects of levothyroxine dosage on fetal thyroid development, we conducted both categorical and continuous analyses (Table 4). We divided patients in the SCH group into low-dose (≤50 mcg/day, n=32) and high-dose (>50 mcg/day, n=18) subgroups. No statistically significant differences were observed in FTC (5.190 ± 1.609 cm vs. 5.104 ± 1.702 cm, p=0.855) or FTA (0.803 ± 0.455 $cm^2$ vs. 0.721 ± 0.502 $cm^2$, p=0.557) between the two dose groups.

Linear regression analysis was performed to further investigate the relationship between levothyroxine dose and fetal thyroid measurements as continuous variables. The regression equations (FTC = 5.570 - 0.007 × Dose; FTA = 0.910 - 0.002 × Dose) indicated a mild negative relationship between dose and thyroid measurements, suggesting a slight decrease in fetal thyroid size with increasing levothyroxine dose. However, these relationships were not statistically significant (p=0.279 for FTC and p=0.149 for FTA), and the coefficients of determination ($R^2$ = 0.028 for FTC and $R^2$ = 0.043 for FTA) indicated that the levothyroxine dose explained only 2.8-4.3% of the variation in fetal thyroid measurements. These findings suggest that the levothyroxine dose does not significantly influence fetal thyroid development in pregnant women treated for subclinical hypothyroidism.

## DISCUSSION

This prospective observational study investigated the relationship between maternal SCH, levothyroxine treatment, and fetal thyroid dimensions in pregnant women. Our findings revealed no significant differences in fetal thyroid measurements between pregnant women with treated SCH and euthyroid controls, suggesting that appropriate levothyroxine treatment may normalize any potential effects of maternal SCH on fetal thyroid development.

Although raw measurements had shown a significantly smaller BPD in fetuses of mothers with SCH (Table 1), standardization using z-scores eliminated this difference (p=0.118), suggesting that the apparent discrepancy was likely


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attributable to minor variations in gestational age distribution between groups rather than a true biological effect of maternal thyroid status.

Our correlation analysis revealed negligible associations between maternal TSH levels and fetal thyroid dimensions (both FTC and FTA), suggesting that maternal thyroid function has no significant effect on fetal thyroid size when appropriately managed with levothyroxine. These findings support the idea that the fetal thyroid gland may develop independently when maternal thyroid dysfunction is effectively controlled.

Notably, our findings revealed a persistently higher AFI in the SCH group even after z-score standardization (0.34 ± 0.81 vs. -0.33 ± 1.00, p<0.001). This observation suggests that maternal thyroid dysfunction may influence fetal fluid homeostasis independently of its effects on structural growth. Several mechanisms could explain this association, including altered renal function due to subtle changes in thyroid hormone levels reaching the fetus, modified placental function affecting fluid exchange, and changes in fetal swallowing and urine production. This finding is particularly interesting because it highlights a potential subclinical manifestation of maternal SCH that persists despite adequate levothyroxine treatment. Previous studies by Mukherjee et al. [18] and Idris et al. [19] reported similar findings regarding amniotic fluid dynamics in pregnancies complicated by thyroid dysfunction, although they primarily focused on overt rather than subclinical hypothyroidism.

Although the correlations between levothyroxine dose and fetal thyroid dimensions did not reach statistical significance, a consistent negative trend was observed. This suggests that higher levothyroxine doses could exert a subtle protective effect against subclinical fetal thyroid enlargement (goiter). While preliminary and hypothesis-generating, this observation warrants further investigation in larger, prospective studies.

Importantly, early detection and treatment of SCH before conception or in the first trimester are critical to ensure optimal thyroid hormone support during the crucial phases of fetal development. However, since our study exclusively included treated SCH cases without an untreated comparator group, definitive conclusions regarding the protective effects of levothyroxine on fetal thyroid organogenesis cannot be reached. Further studies with untreated cohorts are needed to validate this hypothesis.

Early detection and treatment of maternal SCH before conception or during the first trimester are considered essential for supporting normal fetal development, particularly during the early phases of thyroid gland organogenesis. In our study, all patients with SCH had already initiated levothyroxine therapy before or during early pregnancy, potentially mitigating any adverse effects of maternal thyroid dysfunction on fetal thyroid morphology. The absence of significant differences in fetal thyroid dimensions between treated SCH cases and euthyroid controls may reflect the protective influence of timely intervention. However, given that our study did not include an untreated SCH group, we cannot definitively determine whether delayed or absent treatment would have resulted in impaired fetal thyroid development. Therefore, while our findings are encouraging, they should be interpreted with caution. Nevertheless, this approach aligns with prior studies [20–24], which showed that untreated maternal hypothyroidism—whether overt or subclinical—is consistently associated with increased risks of adverse perinatal and neurodevelopmental outcomes, including miscarriage, preterm delivery, fetal growth restriction, and impaired neurocognitive development in offspring.

Our study's findings align with those of Feng et al. [25], who prospectively assessed the impact of maternal hypothyroidism on fetal thyroid development and found no significant differences in fetal thyroid volumes between pregnant women with hypothyroidism and euthyroid controls. Similarly, our study demonstrated that adequately treated SCH did not significantly alter fetal thyroid dimensions. The consistency between these results reinforces the hypothesis that well-managed maternal thyroid dysfunction does not adversely affect fetal thyroid morphology, suggesting that current treatment protocols are effective in ensuring normal fetal thyroid development.

These findings have relevant clinical implications. They suggest that when maternal SCH is appropriately diagnosed and treated early in pregnancy, fetal thyroid development appears unaffected, reinforcing current guideline recommendations for levothyroxine therapy. The observed negative trend between levothyroxine dose and fetal thyroid size, although not statistically significant, raises the possibility that higher doses may contribute to more normalized fetal thyroid morphology. This hypothesis should be explored in future prospective studies with larger sample sizes. Moreover, the consistently elevated AFI observed in the SCH group despite treatment warrants further investigation into the subclinical effects of maternal thyroid dysfunction on fetal fluid regulation. Longitudinal studies incorporating thyroid antibody status, iodine levels, and functional fetal thyroid hormone measurements will provide a comprehensive understanding of maternal-fetal thyroid interactions and guide individualized treatment approaches.

In contrast to Feng et al, our study also explored the correlation between maternal levothyroxine dose and fetal thyroid dimensions, revealing a weak but nonsignificant negative correlation. This suggests that higher levothyroxine doses may have subtle effects on fetal thyroid growth, a hypothesis requiring further validation in larger studies. Although our findings support the safety of levothyroxine therapy in pregnancy, future research should investigate whether prolonged exposure to higher doses affects fetal thyroid function in a clinically meaningful way.


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Beyond maternal hypothyroidism, Luton et al. [26] highlighted the importance of fetal thyroid ultrasonography in pregnancies complicated by Graves' disease and demonstrated that fetal thyroid size, when assessed via ultrasound, can serve as an important marker of fetal thyroid dysfunction. Their results underscore the clinical value of fetal thyroid ultrasound as a diagnostic tool in high-risk pregnancies, reinforcing its potential role in monitoring maternal thyroid disorders during pregnancy.

Despite the clinical significance of this topic, a comprehensive review of the literature revealed a notable paucity of studies evaluating the effects of maternal thyroid dysfunction on fetal thyroid gland morphology using ultrasonographic assessment. Apart from the aforementioned investigations by Feng et al. [25] and Luton et al. [26], there is a substantial gap in research directly examining the relationship between maternal thyroid parameters and fetal thyroid dimensions through imaging modalities. This scarcity of evidence highlights the unique contribution of our study to the existing knowledge base and underscores the need for further investigation in this critical area of maternal-fetal thyroid physiology.

Several methodological strengths enhance the reliability of our findings. First, our prospective observational design with standardized measurement protocols minimized potential measurement bias. Second, the calculation of z-scores to standardize measurements across different gestational ages allowed for more accurate comparisons between groups. Third, the comprehensive assessment of maternal characteristics and detailed evaluation of fetal biometry provided a context for interpreting the thyroid measurements. Fourth, the high interobserver and intraobserver reproducibility (kappa coefficient of 0.85 and ICC of 0.89, respectively) demonstrate the reliability of our ultrasound measurement technique.

### *Limitations*

Nevertheless, our research does include specific constraints that should be considered. First, although our sample size exceeded the minimum required based on power calculations, larger cohorts might detect subtle differences that our study may have missed. Second, we did not administer pretreatment thyroid function tests to all participants, limiting our ability to analyze the impact of pretreatment TSH severity on fetal outcomes. Third, longitudinal measurements throughout pregnancy could have provided comprehensive information about the developmental trajectory of the fetal thyroid gland.

An important limitation of our study was the lack of thyroid antibody (TPOAb/TgAb) data, which could have influenced both maternal thyroid function and fetal thyroid physiology independently. As the 2017 ATA guidelines stratify treatment recommendations based on antibody positivity, future studies should include antibody status to more precisely evaluate maternal-fetal thyroid dynamics.

## CONCLUSION

In conclusion, our prospective observational study demonstrated that maternal SCH, when adequately treated with levothyroxine, does not significantly affect fetal thyroid dimensions. The negligible correlations observed between maternal TSH levels, levothyroxine dose, and fetal thyroid measurements suggest that fetal thyroid development progresses independently once maternal thyroid function is normalized. These findings underscore the importance of early diagnosis and appropriate treatment of SCH, ideally before conception or in the first trimester. Our study contributes valuable data to the limited body of evidence on the ultrasonographic assessment of fetal thyroid development in the context of maternal thyroid dysfunction and provides a foundation for future longitudinal studies exploring the long-term outcomes of these associations.

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**Data Availability Statement:** The underlying data presented in this publication are available upon reasonable request to the corresponding author.

**Ethics Committee Approval:** This research was performed in compliance with the principles outlined in the most recent version of the Declaration of Helsinki (Registration Number: 23-2024 dated October 9, 2024) after approval by the Human Ethics Committee of Haseki Training and Research Hospital.

**Informed Consent:** The purpose and nature of all procedures performed were properly explained to each pregnant woman and she was asked to sign a written informed consent form to participate in this study.

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