e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(4); 270-275

Original Research Article

Maternal and Perinatal Outcomes in Subclinical Hypothyroidism during Pregnancy: A Prospective Comparative Study

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Received: 01-01-2026 / Revised: 15-02-2026 / Accepted: 21-03-2026
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Conflict of interest: Nil

Abstract

Background: Subclinical hypothyroidism (SCH) during pregnancy represents a significant endocrine disorder characterized by elevated thyroid-stimulating hormone (TSH) levels with normal free thyroxine concentrations. The association between SCH and adverse pregnancy outcomes remains controversial, with conflicting evidence regarding maternal and neonatal complications.

Methods: This prospective comparative study enrolled 240 pregnant women (120 with SCH and 120 euthyroid controls) at a tertiary care hospital over an 18-month period. Participants were recruited at ≤20 weeks of gestation and followed until delivery. SCH was defined using trimester-specific TSH thresholds with normal free T4 levels. Primary outcomes included preterm birth, preeclampsia, low birth weight, and neonatal intensive care unit admission. Statistical analysis included chi-square tests, independent t-tests, and multivariate logistic regression.

Results: Women with SCH demonstrated significantly higher rates of preterm birth (26.7% vs 11.7%, p=0.003), preeclampsia (16.7% vs 6.7%, p=0.018), and low birth weight (22.5% vs 9.2%, p=0.005) compared to euthyroid controls. Mean neonatal birth weight was significantly lower in the SCH group (2,680 ± 395 g vs 2,920 ± 365 g, p<0.001). Multivariate analysis revealed SCH as an independent predictor of composite adverse outcomes (adjusted OR 2.14, 95% CI 1.28–3.58, p=0.004).

Conclusion: Subclinical hypothyroidism during pregnancy is associated with significantly increased maternal and perinatal morbidity. Early screening and appropriate management strategies may improve pregnancy outcomes in affected women.

Keywords: Subclinical hypothyroidism, pregnancy outcomes, preterm birth, preeclampsia, thyroid dysfunction, neonatal outcomes.

DOI: 10.25258/ijcpr.18.4.45

Introduction

Thyroid disorders constitute the second most common endocrine abnormality affecting women of reproductive age, with subclinical hypothyroidism representing a particularly prevalent condition during pregnancy [1].

Subclinical hypothyroidism is characterized biochemically by elevated serum thyroid-stimulating hormone concentrations with circulating free thyroxine levels remaining within the normal reference range [2]. The prevalence of this condition during pregnancy varies considerably across different populations, ranging from 2% to 15% depending upon geographic location, iodine

nutritional status, and diagnostic criteria employed [3].

Pregnancy induces profound physiological alterations in thyroid function, including increased thyroid-binding globulin synthesis, enhanced renal iodine clearance, and human chorionic gonadotropin-mediated TSH suppression during the first trimester [4]. These adaptations necessitate the utilization of trimester-specific reference ranges for accurate diagnosis of thyroid dysfunction during gestation [5]. The American Thyroid Association recommends an upper TSH threshold of 2.5 mIU/L during the first trimester and 3.0 mIU/L during subsequent trimesters when population-specific reference ranges are unavailable [6].

The clinical significance of subclinical hypothyroidism during pregnancy has been extensively investigated, with observational studies demonstrating associations with various adverse outcomes including spontaneous abortion, preterm delivery, gestational hypertensive disorders, low birth weight, and impaired neurocognitive development in offspring [7].

A comprehensive meta-analysis by Maraka and colleagues reported significantly elevated odds of pregnancy loss and preterm birth among women with untreated subclinical hypothyroidism [8]. Furthermore, maternal thyroid dysfunction has been implicated in altered placental development and fetal growth restriction through mechanisms involving impaired trophoblast invasion and placental angiogenesis [9].

However, evidence regarding the benefits of levothyroxine treatment in subclinical hypothyroidism remains inconclusive. The Controlled Antenatal Thyroid Screening (CATS) study failed to demonstrate significant improvements in offspring neurodevelopmental outcomes following treatment [10]. Similarly, subsequent randomized controlled trials have yielded conflicting results regarding obstetric outcomes [11]. This heterogeneity in findings may be attributable to variations in diagnostic thresholds, timing of intervention initiation, and the presence of thyroid autoantibodies [12]. The presence of anti-thyroid peroxidase antibodies has been identified as an independent risk factor for adverse pregnancy outcomes, even in euthyroid women [13].

Studies have demonstrated that autoimmune thyroiditis may exacerbate the risks associated with subclinical hypothyroidism through additional immunological mechanisms [14]. Consequently, comprehensive assessment of thyroid function during pregnancy should incorporate evaluation of autoantibody status.

In developing countries, particularly India, the burden of thyroid disorders during pregnancy is substantial, with reported prevalence rates of subclinical hypothyroidism ranging from 5% to 14% [15]. The heterogeneity in available data and the potential public health implications underscore the necessity for additional evidence from prospective studies with adequate statistical power.

The primary aim of this study was to compare maternal and perinatal outcomes between pregnant women diagnosed with subclinical hypothyroidism and matched euthyroid controls in a tertiary care setting.

Materials and Methods

Study Design and Setting: This prospective comparative study was conducted at the Department of Obstetrics and Gynaecology, Basaveshwara Medical College and Hospital, Chitradurga, India, over an 18-month period from January 2023 to June 2024.

Sample Size Calculation: Sample size estimation was performed for comparison of two independent proportions based on the primary outcome of composite adverse pregnancy outcomes. Utilizing data from previous literature suggesting adverse outcome rates of approximately 28% in subclinical hypothyroidism and 12% in euthyroid pregnancies, with a two-sided alpha of 0.05 and statistical power of 80%, the required sample size was calculated as 108 participants per group. Accounting for an anticipated 10% attrition rate, the target enrollment was established at 120 participants in each group, yielding a total sample size of 240 pregnant women.

Participant Selection: Consecutive pregnant women presenting to the antenatal clinic at ≤20 weeks of gestation were screened for eligibility. Inclusion criteria comprised: singleton pregnancy, maternal age between 18 and 40 years, gestational age ≤20 weeks at enrollment, and confirmed diagnosis of either subclinical hypothyroidism (cases) or normal thyroid function (controls). Subclinical hypothyroidism was defined as serum TSH exceeding trimester-specific upper limits (>2.5 mIU/L in first trimester; >3.0 mIU/L in second trimester) with free T4 within normal reference range.

Exclusion criteria included: pre-existing thyroid disorders requiring treatment prior to conception, overt hypothyroidism or hyperthyroidism, multiple gestation, pre-gestational diabetes mellitus, chronic hypertension, chronic renal disease, autoimmune disorders other than thyroid autoimmunity, and concurrent use of medications known to affect thyroid function.

Data Collection and Follow-up: At enrollment, comprehensive baseline data were collected including demographic characteristics, obstetric history, anthropometric measurements, and medical

history. Laboratory investigations included serum TSH, free T4, and anti-thyroid peroxidase antibody measurements. Blood samples were collected following overnight fasting and analyzed using chemiluminescent immunoassay methodology. Participants received standard antenatal care according to institutional protocols.

Women diagnosed with subclinical hypothyroidism were managed according to prevailing guidelines, with levothyroxine therapy initiated at the discretion of the treating physician based on TSH levels and antibody status. All participants were followed throughout pregnancy with regular antenatal visits and monitored for development of complications.

Outcome Measures: Primary maternal outcomes included: preeclampsia (defined as new-onset hypertension after 20 weeks with proteinuria or end-organ dysfunction), gestational hypertension, gestational diabetes mellitus, and mode of delivery. Primary perinatal outcomes comprised: preterm birth (<37 completed weeks), low birth weight (<2500 g), Apgar scores at 1 and 5 minutes, neonatal intensive care unit admission, and stillbirth.

Statistical Analysis: Data were analyzed using Statistical Package for Social Sciences version 26.0 (IBM Corp, Armonk, NY). Continuous variables were assessed for normality using the Shapiro-Wilk test and expressed as mean ± standard deviation. Categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using independent samples t-test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was conducted to identify independent predictors of adverse outcomes after adjusting for potential confounders. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 240 pregnant women were enrolled and completed the study, comprising 120 women with subclinical hypothyroidism and 120 euthyroid controls. The mean gestational age at enrollment was 13.2 ± 3.4 weeks, with no significant difference between groups.

Baseline Characteristics: The baseline demographic and clinical characteristics of the study population are presented in Table 1. The two groups were comparable with respect to maternal age, parity, body mass index, and gestational age at enrollment.

The mean TSH concentration was significantly elevated in the SCH group compared to controls (4.52 ± 1.18 mIU/L vs 1.74 ± 0.58 mIU/L, p<0.001), while free T4 levels were similar between groups. Anti-TPO antibody positivity was observed in 42 (35.0%) women with SCH compared to 14 (11.7%) euthyroid controls (p<0.001).

Table 1: Baseline Demographic and Laboratory Characteristics

Parameter	SCH Group (n=120)	Euthyroid Group (n=120)	p-value
Maternal age (years)	26.4 ± 4.2	26.8 ± 3.8	0.438
Primigravida, n (%)	68 (56.7%)	64 (53.3%)	0.592
Body mass index (kg/m²)	25.8 ± 3.6	25.4 ± 3.9	0.407
Gestational age at enrollment (weeks)	12.8 ± 3.2	13.4 ± 3.1	0.148
Serum TSH (mIU/L)	4.52 ± 1.18	1.74 ± 0.58	<0.001
Free T4 (pmol/L)	14.8 ± 2.2	15.4 ± 1.8	0.062
Anti-TPO positive, n (%)	42 (35.0%)	14 (11.7%)	<0.001

Maternal Outcomes: Maternal outcomes are summarized in Table 2. Women with subclinical hypothyroidism demonstrated significantly higher rates of preeclampsia (16.7% vs 6.7%, p=0.018) and cesarean delivery (45.8% vs 33.3%, p=0.047) compared to euthyroid controls. The incidence of gestational hypertension was elevated in the SCH group, although this difference did not achieve statistical significance (10.8% vs 6.7%, p=0.253).

Gestational diabetes mellitus occurred with similar frequency in both groups.

Table 2: Maternal Outcomes

Outcome	SCH Group (n=120)	Euthyroid Group (n=120)	p-value
Preeclampsia, n (%)	20 (16.7%)	8 (6.7%)	0.018
Gestational hypertension, n (%)	13 (10.8%)	8 (6.7%)	0.253
Gestational diabetes, n (%)	12 (10.0%)	10 (8.3%)	0.657
Cesarean delivery, n (%)	55 (45.8%)	40 (33.3%)	0.047
Postpartum hemorrhage, n (%)	8 (6.7%)	5 (4.2%)	0.395
Composite maternal adverse outcome, n (%)	26 (21.7%)	12 (10.0%)	0.014

Perinatal Outcomes: Perinatal outcomes demonstrated significant differences between groups (Table 3).

The incidence of preterm birth was substantially higher in women with subclinical hypothyroidism compared to euthyroid controls (26.7% vs 11.7%, p=0.003). Similarly, low birth weight occurred more frequently in the SCH group (22.5% vs 9.2%, p=0.005). Mean neonatal birth weight was significantly lower in infants born to mothers with SCH (2,680 ± 395 g vs 2,920 ± 365 g, p<0.001). Neonatal intensive care unit admission rates were elevated in the SCH group (18.3% vs 8.3%, p=0.024). No significant differences were observed in Apgar scores or stillbirth rates between groups.

Table 3: Perinatal Outcomes

Outcome	SCH Group (n=120)	Euthyroid Group (n=120)	p-value
Preterm birth (<37 weeks), n (%)	32 (26.7%)	14 (11.7%)	0.003
Low birth weight (<2500 g), n (%)	27 (22.5%)	11 (9.2%)	0.005
Mean birth weight (g)	2,680 ± 395	2,920 ± 365	<0.001
Apgar score <7 at 5 min, n (%)	9 (7.5%)	5 (4.2%)	0.274
NICU admission, n (%)	22 (18.3%)	10 (8.3%)	0.024
Stillbirth, n (%)	2 (1.7%)	1 (0.8%)	0.562

Multivariate logistic regression analysis, adjusting for maternal age, parity, BMI, and anti-TPO antibody status, confirmed subclinical hypothyroidism as an independent predictor of composite adverse pregnancy outcomes (adjusted OR 2.14, 95% CI 1.28–3.58, p=0.004).

Discussion

The present prospective comparative study demonstrates a significant association between subclinical hypothyroidism during pregnancy and adverse maternal and perinatal outcomes. Women with SCH exhibited substantially elevated rates of preeclampsia, preterm birth, low birth weight, and neonatal intensive care unit admission compared to euthyroid controls. These findings contribute to the growing body of evidence supporting the clinical significance of subclinical thyroid dysfunction during gestation.

Our observation of increased preterm birth rates in women with subclinical hypothyroidism aligns with findings from previous large-scale investigations. A population-based cohort study by Korevaar and colleagues demonstrated that maternal hypothyroxinemia and elevated TSH concentrations were independently associated with preterm delivery [16]. The pathophysiological mechanisms underlying this association likely involve thyroid hormone-mediated effects on placental development and function. Thyroid hormones regulate trophoblast differentiation, placental angiogenesis, and the expression of genes essential for normal placentation [17]. The significantly higher incidence of preeclampsia observed in the SCH group corroborates findings from multiple observational studies. Wilson and colleagues reported a dose-response relationship between maternal TSH concentrations and preeclampsia risk in a large retrospective cohort [18]. Endothelial dysfunction, a hallmark of preeclampsia pathogenesis, may be exacerbated by subclinical hypothyroidism through mechanisms involving altered nitric oxide synthesis and increased oxidative stress [19]. Furthermore, the association between thyroid autoimmunity and systemic inflammation may contribute to the heightened preeclampsia risk observed in our cohort.

The reduced mean birth weight and increased low birth weight rates among infants born to mothers with SCH are consistent with evidence from prospective studies examining the relationship between maternal thyroid function and fetal growth. Medici and colleagues demonstrated that maternal TSH levels were inversely associated with birth weight in a large population-based cohort [20]. Thyroid hormones play a crucial role in fetal growth and development, with maternal thyroxine representing the primary source of thyroid hormone for the fetus during early gestation [21].

The elevated anti-TPO antibody positivity rate observed in the SCH group warrants particular attention. Thyroid autoimmunity has been identified as an independent risk factor for adverse pregnancy outcomes, potentially through mechanisms distinct from thyroid hormone insufficiency [22]. The immunological dysregulation associated with autoimmune thyroiditis may impair implantation, placental development, and maintenance of pregnancy through effects on local immune tolerance [23]. Our multivariate analysis, which adjusted for anti-TPO status, demonstrated that SCH remained an independent predictor of adverse outcomes, suggesting that both hormonal and immunological factors contribute to pregnancy complications.

The clinical implications of our findings support the consideration of universal thyroid screening during early pregnancy. While controversy persists regarding screening strategies, the substantial

burden of adverse outcomes associated with undetected thyroid dysfunction argues for routine assessment [24]. Early identification of subclinical hypothyroidism enables timely initiation of levothyroxine therapy when indicated and enhanced surveillance for pregnancy complications. Casey and colleagues emphasized the importance of early detection and treatment to optimize pregnancy outcomes in women with thyroid dysfunction [25].

Several limitations of this study merit consideration. The single-center design may limit generalizability to other populations with different demographic characteristics and iodine nutritional status. Long-term neurodevelopmental outcomes in offspring were not assessed, precluding conclusions regarding the developmental implications of maternal SCH. Additionally, treatment protocols for subclinical hypothyroidism were not standardized, potentially introducing variability in outcomes.

Conclusion

This prospective comparative study demonstrates that subclinical hypothyroidism during pregnancy is significantly associated with increased rates of preeclampsia, preterm birth, low birth weight, and neonatal intensive care unit admission. Subclinical hypothyroidism emerged as an independent predictor of composite adverse pregnancy outcomes after adjustment for potential confounders.

These findings underscore the importance of early thyroid function screening during pregnancy and appropriate management of affected women. Implementation of routine screening protocols and individualized treatment strategies may contribute to improved maternal and perinatal outcomes. Future multicenter randomized controlled trials are warranted to establish optimal screening, diagnostic, and therapeutic approaches for subclinical hypothyroidism in pregnancy.

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