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Subclinical Hypothyroidism among Pregnant Women with First Trimester Pregnancy Loss

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ABSTRACT

Background: Subclinical hypothyroidism, defined by elevated thyroid-stimulating hormone levels with normal free thyroxine, is prevalent in pregnancy and has been associated with adverse outcomes, including first-trimester pregnancy loss. **Aim and objectives:** This study aimed to evaluate the impact of subclinical hypothyroidism on women experienced spontaneous miscarriage at first trimester.

Patients and methods: This case-control investigation has been performed on one hundred pregnant women recruited from The Outpatient (Antenatal Care Clinic) and Emergency Room at El Sahel Teaching Hospital through the period from March 2024 to February 2025. They were divided into two groups: Group A (Miscarriage group): 50 women presented with first trimester spontaneous miscarriage either missed, anembryonic sac, inevitable, complete, or incomplete miscarriage diagnosed by ultrasound or clinically and group B (Control group): 50 women with healthy viable pregnancy of gestational age < 20 weeks. **Results:** There was a significant variance among both groups as regards thyroid profile where group A had significantly greater TSH levels compared to group B ($P < 0.001$). There was a significant variance among both groups as regards the prevalence of subclinical hypothyroidism, which was significantly higher in group A compared to group B.

Conclusion: Subclinical hypothyroidism throughout pregnancy has been related to several negative maternal outcomes and may elevate the risk of first-trimester pregnancy loss. Early intervention with LT4 therapy, especially in women with higher TSH levels, may mitigate this risk. Further studies are warranted to establish definitive treatment.

Keywords: Subclinical hypothyroidism, Spontaneous miscarriage, Thyroid dysfunction.

INTRODUCTION

Thyroid disorders represent the second most common endocrine condition in pregnant women, following diabetes mellitus in which variable physiological alterations affect thyroid function [(1)]. In pregnancy, serum concentration of thyroid-stimulating hormone (TSH) is mostly utilized for evaluating thyroid and detecting thyroid dysfunction [(2)]. Subclinical hypothyroidism (SCH) is a prevalent thyroid illness that occurs throughout pregnancy. It is defined by elevated (TSH) levels with normal concentrations of free thyroxine (FT4) [(3)]. During the first three months in pregnancy, the baby count on the mother's thyroid hormone (T4), which passes through the placenta. Around week's ten to twelve of gestation, the fetus begins to produce its own thyroid hormone [(4)]. Subclinical hypothyroidism can lead to negative effects on the mother's health, as well as problems throughout childbirth and impaired development of the fetal nervous system in the early stages of pregnancy, due to the insufficient presence of thyroid hormone [(5)].

A meta-analysis indicated that SCH in early pregnancy is linked to a greater likelihood of developing pre-eclampsia and an increased rate of perinatal death. However, there is no association between SCH and miscarriage [(6)]. Nevertheless, there have been reports indicating that women with SCH and elevated levels of maternal thyroid-stimulating hormone in their blood are more likely to experience miscarriage when compared to women who are not affected by this condition [(7)]. Hence, the association between SCH and the chance of miscarriage remains to be a subject of controversy.

According to the 2011 American Thyroid Association (ATA) recommendations, the upper reference limit for TSH in the first trimester of pregnancy was defined as 2.5 mU/L [(8)]. Further studies have shown considerable differences in TSH and FT4 reference ranges across various populations. Notably, about 90% of these studies found upper TSH limits exceeding the 2.5 mU/L threshold. Such discrepancies may increase the likelihood of misdiagnosing overt hypothyroidism and (SCH) during pregnancy. Consequently, the 2017 ATA guidelines recommended using an upper TSH limit of 4.0 mU/L, acknowledging the absence of universally applicable pregnancy-specific reference ranges [9].

The Aim of this investigation was to monitor the occurrence of SCH in pregnant women experienced spontaneous miscarriage at first trimester.

PATIENTS AND METHODS

This case-control research was implemented on one hundred pregnant females recruited from The Outpatient Clinic, Department of Gynecology and Obstetrics in El Sahel Teaching Hospital through the period from March 2024 to February 2025. They were separated into two groups: Group A (Miscarriage group): 50 women presented with first trimester spontaneous miscarriage either missed, anembryonic sac, inevitable, complete, or incomplete miscarriage diagnosed by ultrasound or clinically and group B (Control group): 50 women with healthy viable pregnancy of gestational age < 20 weeks.

Estimation of sample size: The sample size was determined using MedCalc® software version 12.3.0.0

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(Ostend, Belgium), applying a 95% confidence level, 80% statistical power, and a 5% alpha error, based on findings from earlier research of **Li *et al*.** [10], which exhibited that in females experienced first trimester spontaneous miscarriage, there was evidence for a positive correlation of increased TSH serum level suggesting prevalence of SCH (case group). Specifically, the PI correlated positively with TSH (p-value). This study was based on estimated odds ratio = 1.115. The final maximum sample size taken from the Epi- Info output was one hundred.

Inclusion criteria: Women between 18 and 40 years old with a single intrauterine pregnancy of less than 20 weeks' gestation. The gestational age was assessed using the date of the last menstrual period and/or ultrasound evaluation. Miscarriage has been recorded with ultrasonographic confirmation or clinical presentation.

Exclusion criteria: Cases who had multiple pregnancies, any thyroid disorders, diabetes, abnormal liver enzymes and any other chronic illness as well as patients who were taking medications that may impact thyroid function, like dopamine, glucocorticoids, antiepileptic medications, anticoagulants and tricyclics, or selective serotonin reuptake inhibitors (SSRIs).

Methods: 8-ml blood sample was collected from each patient, then was divided according to type of tube and test. Thyroid function tests TSH and fT4: The initial 2 ml of blood were collected into a serum vacutainer tube with gel, allowed to clot, and centrifuged at 3,000 rpm for up to 10 minutes to obtain serum. The separated serum or plasma was maintained at +15 °C to +30 °C for no longer than eight hours. If assays were delayed beyond eight hours, samples were stored at +2 °C to +8 °C. Thyroid function tests were performed using the Tosoh AIA-360 Automated Immunoassay Analyzer, which automatically executed all required calculations to generate the final results. The system software applied a weighted four-parameter logistic curve (4PLC) model, utilizing calibration data and the measured light emission to determine analyte concentrations in the samples.

Routine laboratory investigation: Complete blood picture, D-dimer, the international normalized ratio (INR), protein C, protein S and clotting time (CT). Thrombophilia tests were done to exclude any causes could be a reason for miscarriage at first trimester.

Parameters of Ultrasound: The gestational sac is usually detectable by 5–6 weeks of pregnancy using transabdominal or transvaginal ultrasound. The mean sac diameter (MSD), calculated as (length + height + width)/3, generally measures 2–4 mm greater than the gestational age in weeks. By 5.5–6 weeks, a yolk sac should be visible in the gestational sac. It appears as a round, echogenic structure, thick-walled with an anechoic center. Yolk sac measurement is performed via transabdominal ultrasound when the MSD reaches 20 mm or at approximately 7 weeks of gestation, and via transvaginal ultrasound when the MSD is 8–10 mm or at around 5.5 weeks. A fetal pole should be evident by 6–7 weeks, with crown–rump length used for measurement. Cardiac activity is typically detectable by 6–7 weeks, serving as a key indicator of pregnancy viability.

Miscarriage confirmation: Ultrasonographic miscarriage confirmation is based on specific morphometric criteria and the absence of embryonic development. A definitive diagnosis can be established by observing a mean gestational sac diameter exceeding 25 mm without a yolk sac, or a fetal pole with a crown-rump length of 7 mm or more lacking cardiac activity. Findings suggestive of an impending or incomplete miscarriage include the visualization of fetal tissues or a heterogeneous intrauterine mass indicative of retained products of conception (RPOC). Doppler ultrasonography enhances diagnostic accuracy by detecting vascularity within the retained tissue. However, in more protracted cases, the RPOC may become avascular. When findings are equivocal, a follow-up scan after a one-to-two-week interval is recommended to confirm the absence of intrauterine growth and establish a conclusive diagnosis.

Outcome measure(s): Pregnancy confirmation and calculation of gestational age by ultrasound and last menstrual period. Measures of TSH and fT4 to find prevalence of thyroid function in first trimester spontaneous miscarriage. SCH has been described as elevated serum TSH levels and normal fT4. The updated ATA guidelines were used. According to it, the upper reference limit of 4.0 mU/L at first trimester pregnancy.

Ethics approval: The study proposal was reviewed and approved by The General Organization for Teaching Hospitals and Institutes Research Ethics Committee (no. HS000135 on 22/1/2025). Throughout the course of the investigation, the Helsinki Declaration was adhered to. Written informed consents were obtained from all participants.

Statistical analysis

The collected data were processed and analyzed using SPSS software version 28 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, while categorical data were described as numbers and percentages. Differences between groups were evaluated using the independent samples t-test for quantitative variables and the Chi-square (χ^2) test for qualitative ones. When any expected frequency was below 5, Fisher's exact test was utilized. Logistic regression was applied to identify factors independently associated with SSI. Statistical significance was defined at a p-value of ≤ 0.05.

RESULTS

Table (1) demonstrated no significant variance between groups regarding residence, occupation, maternal age, gestational age, weight, height, BMI, smoking, previous history of family miscarriages and history with thyroid disease.

Table (1): General demographic data of the examined groups

		Group A (n=50)	Group B (n=50)	P value
Residence	**Urban**	27 (54%)	26 (52%)	1.000
	Rural	23 (46%)	24 (48%)	
Occupation	**Working**	30 (60%)	33 (62%)	0.679
	Housewife	20 (40%)	17 (38%)	
Maternal age (years)	**Mean ± SD**	27.5 ± 5.8	26.1 ± 6.7	0.267
Gestational age	**Range**	7 (4-9)	7 (4-9)	1.000
Weight (Kg)	**Mean ± SD**	81.7 ± 9.4	80.3 ± 11.6	0.509
Height (m)	**Mean ± SD**	1.64 ± 0.05	1.62 ± 0.04	0.073
BMI (Kg/m^2)	**Mean ± SD**	29.42± 3.00	28.88±3.43	0.42
Smoking	**Yes**	39 (78%)	41 (82%)	0.793
	No	11 (22%)	9 (18%)	
Previous History of Miscarriage	**Yes**	9 (18%)	10 (20%)	0.793
	No	41 (82%)	40 (80%)	
Family history with thyroid disease	**Yes**	5 (10%)	2 (4%)	0.431
	No	45 (90%)	48 (96%)	

BMI: Body mass index

The groups were comparable in serum protein C, protein S, and free T4 levels. In contrast, the thyroid profile revealed a statistically significant disparity, with group A exhibiting markedly elevated TSH levels ($p < 0.001$) and a higher incidence of SCH than group B (Table 2).

Table (2): Thrombophilia examination and thyroid profile in the examined groups

		Group A (n=50)	Group B (n=50)	P value
Protein C (U/ml)	**Mean ± SD**	0.94 ± 0.08	0.96 ± 0.1	0.69
Protein S (U/ml)	**Mean ± SD**	1.1 ± 0.22	1.2 ± 0.22	0.08
TSH (mIU/L)	**Mean ± SD**	3.7 ± 0.19	2.2 ± 0.21	<0.001*
Free T4 (pmol/L)	**Mean ± SD**	16.7 ± 2.69	17± 3.01	0.71
Subclinical hypothyroidism	**Yes**	21 (42%)	10 (20%)	0.017*
	No	29 (58%)	40(80%)	

TSH: Thyroid-stimulating hormone, ***:** statistically significant as $p \leq 0.05$

On multiple regression analysis, table (3) showed that a significant distinction was observed among both groups regarding TSH in which higher TSH in group A than in group B giving a significant predictor of miscarriage (P= 0.007 and < 0.001 respectively).

Table (3): Multivariate regression analysis for the prediction of subclinical hypothyroidism

Variable	Coefficient	Std. Error	Odds ratio	95% CI	P
Gestational age	0.079	0.065	1.093	0.898 - 1.191	0.21
Maternal age	0.045	0.037	1.051	0.98 – 1.14	0.25
BMI	0.50801	0.48491	1.6450	0.6115 - 4.4272	0.30
TSH	2.0551	0.49725	7.8108	2.4705 - 23.6931	<0.001*
Free T4	-0.17389	0.11871	0.7787	0.7625 to 1.1021	0.16
Family history with thyroid disease	0.75138	0.89421	2.1723	0.2485 - 11.4975	0.38
Smoking	0.39781	0.49887	1.646	0.5768 - 4.1421	0.41

TSH: Thyroid-stimulating hormone, ***:** statistically significant as $p \leq 0.05$

DISCUSSION

This investigation was to assess the occurrence of SCH among women with first-trimester spontaneous miscarriage. Baseline analysis confirmed that the groups were well-matched, with no significant differences in key covariates such as residence, occupation, maternal age, weight, height, BMI, or smoking history.

Similarly**, Kiran *et al.*** [11] cross-sectional retrospective study on 718 cases found no significant association between baseline characteristics and preconception TSH groups. The study reported that maternal outcomes were not significantly influenced by baseline characteristics such as age, BMI, and smoking status. Similarly, **Li J *et al.*** [12] analyzed 421 cases and 1,684 controls and reported no significant differences in previous miscarriage history, family history of thyroid disease, or laboratory parameters including INR, D-dimer, protein C and protein S. These findings reinforce that baseline characteristics were comparable, reducing potential confounding in the evaluating thyroid function and miscarriage risk.

The current study revealed a clear difference in serum TSH levels between the two groups. Women in group A (cases) exhibited significantly higher TSH concentrations compared with group B (controls) ($p < 0.001$). In group A, TSH values ranged from 1.5 to 4.9 mIU/L, with a mean of 3.7 ± 1.09 mIU/L, whereas group B ranged from 1 to 4.3 mIU/L, with a mean of 2.2 ± 0.91 mIU/L. Conversely, free T4 concentrations did not differ significantly, with mean values of 16.7 ± 2.69 pmol/L in group A and 17 ± 3.01 pmol/L in group B ($p = 0.71$).

This outcome aligns with recent research by **Li *et al.*** [13] who reported that the greater TSH levels than the normal range the more increase risk of thyroid antibody positivity in adults Additionally, a study by **Jäger *et al.*** [14] detected that elevated TSH levels were prevalent among patients undergoing repeated testing, indicating potential clinical significance.

Regarding free T4 levels, our study found no significant difference between groups (Group A: 16.7 pmol/L, Group B: 17 pmol/L, p=0.71). This is consistent with findings of **Heald *et al.*** [15] who observed that free T4 levels did not significantly differ between groups in their research on thyroid hormone profiles. Conversely, **Li *et al.*** [13] reported higher free T4 levels in individuals with elevated TSH, suggesting a complex interplay between these hormones.

A reciprocal relationship has been observed between thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG) levels. Lower concentrations of hCG may contribute to pregnancy loss. Studies indicate that elevated TSH levels in first trimester are linked with high risk of pregnancy loss [13].

Additionally, **Khan *et al.*** [16] reported that out of 457 participants in their study, 169 had TSH levels between 4.6 and 10 mIU/L, while 288 exhibited TSH below 4 mIU/L. The prevalence of SCH among pregnant women during the first trimester was estimated at 37%.

According to the multiple regression model, group A showed significantly elevated thyroid-stimulating hormone (TSH) levels relative to group B, a factor that constituted a significant predictor of miscarriage ($p < 0.001$). This finding aligns with recent studies, such as **Sharma *et al.*** [17] who reported that higher maternal TSH levels are linked with increased risk of pregnancy loss and adverse outcomes.

Also, our findings align with the research conducted by **Maraka *et al.*** [18] which indicated that SCH throughout pregnancy has been related to several adverse effects for both the mother and baby.

Conversely, some investigations did not detect a direct connection between thyroid hormone levels and miscarriage, highlighting that variations in study populations, diagnostic criteria, or sample sizes may account for discrepancies [19]. Also, **Islam *et al.*** [20] found that SCH was a common endocrine disorder during pregnancy, but did not specifically associate it with miscarriage. This indicates that while prevalent, SCH may not directly contribute to pregnancy loss in all populations.

A separate investigation conducted by **Mannisto T *et al.*** [21] showed that the presence of thyroid dysfunction & antibodies during pregnancy can serve as indicators for the development of thyroid illness in the future. Furthermore, the presence of overt hypothyroidism appeared to be indicative of a subsequent risk of developing diabetes.

CONCLUSION

Cases with SCH was found to have miscarriage. Pregnant women exhibiting higher TSH concentrations were found to have a greater likelihood of experiencing miscarriage during early gestation.

Availability of data and materials: Necessary datasets validating the findings of this research can be acquired from the relevant author upon a valid request. Data access was subject to institutional data-sharing policies and ethical guidelines.

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Conflict of interest: No conflicts of interest.

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