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Frequency of undiagnosed subclinical and overt hypothyroidism in pregnant women of Pakistan

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Abstract
Objective: To determine the frequency of undiagnosed sub-clinical and overt hypothyroidism among pregnant women in Pakistan and assess associated obstetric characteristics.
Methodology: This prospective, multicenter observational study was conducted from February to October 2024 across tertiary care hospitals in Pakistan. A total of 1,200 pregnant women aged 18-45 years, in any trimester, were enrolled. Women with known thyroid disorders, autoimmune conditions, or use of thyroid-affecting medications were excluded. Clinical data were recorded using a structured proforma. Blood samples were analyzed for serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), and thyroid peroxidase antibodies (anti-TPO). Subclinical hypothyroidism (SCH) was defined as TSH 2.5-10 mIU/L with normal FT4; overt hypothyroidism was defined as TSH ≥ 10 mIU/L or low FT4. Data were analyzed using SPSS v20 with significance set at $p<0.05$.
Results: The 1,200 participants, the mean age was 27.45±5.15 years and mean gestational age was 25.51±8.72 weeks. Thyroid dysfunction was detected in 12.4% of women, with 9.3% having SCH and 3.1% overt hypothyroidism. A significant positive correlation was observed between TSH and anti-TPO levels (r=0.204, $p<0.001$). Adverse obstetric outcomes were notable: 29.3% had a history of miscarriage, 6.1% reported intrauterine death, 7.5% neonatal death, and 6% preterm birth. Anti-TPO antibodies were elevated in a proportion of women, even among those who were euthyroid. No significant associations were found between thyroid dysfunction and gestational diabetes, pre-eclampsia, or macrosomia in this cohort.
Conclusion: Subclinical hypothyroidism is a prevalent and frequently undiagnosed condition among pregnant women in Pakistan. Given its potential link with adverse pregnancy outcomes, routine antenatal thyroid screening especially in women with risk factors or high anti-TPO titers should be considered. Larger prospective studies are needed to evaluate the long-term impact of maternal thyroid autoimmunity in euthyroid women.

Keywords: Thyroid-Stimulating Hormone (TSH), subclinical hypothyroidism, anti-thyroid peroxidase antibodies, pregnancy outcomes, antenatal screening

Introduction

Pregnancy is associated with a number of physiological changes, including significant alterations in circulating thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels, particularly during the first trimester [1]. Maternal thyroid hormone levels generally normalize as the fetal thyroid begins to function and produce its own hormones later in gestation [2]. Thyroid hormones are essential for fetal neurological development, especially during early pregnancy when the fetus is entirely dependent on maternal supply. Hypothyroidism during pregnancy whether overt or subclinical is associated with multiple adverse maternal and fetal outcomes if left undiagnosed and untreated. These complications include miscarriages, congenital anomalies, preterm labor, Intrauterine Growth Restriction (IUGR), Low Birth Weight (LBW), placental abruption, Postpartum Hemorrhage (PPH), and Respiratory Distress Syndrome (RDS) in newborns.

Subclinical hypothyroidism (SCH), defined by elevated trimester-specific TSH levels with normal FT4, is often asymptomatic but may occasionally present with mild symptoms such as fatigue or constipation. According to the American Thyroid Association (ATA) 2017 guidelines, treatment is recommended for pregnant women with TSH > 2.5 mIU/L and positive Thyroid Peroxidase Antibodies (TPOAb) [3]. Hypothyroidism affects approximately 2-3% of pregnancies, with overt hypothyroidism present in about 0.3-0.5% and SCH in 2-2.5% [4].

Additionally, 5-10% of pregnant women are positive for TPO antibodies, placing them at increased risk for thyroid dysfunction during pregnancy. SCH is thought to complicate 1-2% of all pregnancies based on population- and trimester-specific reference ranges [5]. The presence of TPO antibodies, even with normal FT4 levels, is a known risk factor for developing thyroid disease and may warrant trimester-specific monitoring [6]. Evidence suggests that adverse pregnancy outcomes associated with thyroid dysfunction may become clinically relevant at a TSH threshold > 2.5 mIU/L in the first trimester, rather than relying solely on percentile-based reference intervals [7].

Given the potential burden of subclinical hypothyroidism in pregnancy and the possibility of improving outcomes through early detection and treatment, there is growing support for routine screening. Therefore, the objective of this multicenter study was to determine the frequency of subclinical and overt hypothyroidism among pregnant women in Pakistan. The ultimate goal is to assess the burden of SCH and inform future recommendations for routine antenatal screening and management guidelines to improve maternal and neonatal outcomes.

Methodology

This prospective, Pan Pakistan multicenter observational study was conducted across selected tertiary care hospitals in Pakistan, including centers from all four provinces and the federal capital. The study was conducted from February 2024 to October 2024 after taking IREB approval from Baqai Medical University and followed a standardized protocol across all participating sites to ensure consistency in data collection and laboratory analysis. A total of approximately 1,200 pregnant women were enrolled using a non-probability consecutive sampling technique. Women were eligible for inclusion if they were between 18 and 45 years of age, in any trimester of pregnancy regardless of gravida or parity status, and willing to provide written informed consent along with a blood sample. Women were excluded if they had a prior diagnosis of thyroid dysfunction, were using medications that could interfere with thyroid function (such as levothyroxine, methimazole, iodide, lithium, amiodarone, or corticosteroids), or had known autoimmune diseases including connective tissue disorders.

Data were collected using a predesigned structured proforma that included sociodemographic details, obstetric history, physical examination findings, and results of relevant investigations including obstetric ultrasound and thyroid function tests. After obtaining consent, blood samples were collected from each participant and analyzed for Serum Thyroid-Stimulating Hormone (TSH), Free Thyroxine (FT4), and Thyroid Peroxidase (TPO) antibodies. All laboratory assessments were conducted using the same assay methods and standardized protocols across all centers to ensure comparability.

Thyroid function was interpreted using trimester-specific reference ranges in accordance with the American Thyroid Association (ATA) 2017 [3] guidelines. Subclinical hypothyroidism (SCH) was defined as a TSH level between 2.5 and 10 mIU/L with a normal FT4, while overt hypothyroidism was defined as a TSH ≥ 10 mIU/L or an elevated TSH with a reduced FT4.

All data were entered into a secure electronic database using unique identifiers to maintain participant confidentiality. Data were validated through double entry and routine quality checks. Descriptive statistics were applied to calculate the prevalence of subclinical and overt hypothyroidism.

Statistical Analysis

The SPSS.20 was used to do the analysis of the study data, and a P-Value < 0.05 was considered statistically significant. Descriptive analysis and Correlation test were applied, data presented as percentages, mean and standard deviations, and Correlation.

Results

A total of 1,200 pregnant women were enrolled in the study. The majority of participants were aged between 26-35 years (53.8%), followed by 18-25 years (40.1%), and a smaller proportion aged 36-45 years (6.1%). The mean age of the study population was 27.45±5.15 years. Participants had an average weight of 66.78±13.33 kg and a mean height of 158.69±6.54 cm, yielding a mean BMI of 26.50±5.10 kg/m². Regarding antenatal care, 76.3% of participants were booked, and 23.8% were unbooked at the time of data collection.Thyroid function parameters showed a mean TSH level of 1.579±1.80 µU/mL, mean FT4 level of 0.92±0.51 ng/dL, and mean anti-TPO antibody level of 20.93±82.20 IU/mL (Table 1).

Table 1: Baseline characteristics of study participants.

Descriptive Statistics		
Variables	Mean	Std. Deviation
Age	27.45	5.153
Gestational Age (Weeks)	25.51	8.718
Pulse (bpm)	84.82	8.898
Weight (Kg)	66.78	13.325
Height (cm)	158.69	6.536
BMI Kg/m2	26.50	5.102
TSH (µU/mL)	1.5798	1.80127
FT4 (ng/dL)	.9268	.51861
TPO (IU/mL)	20.9331	82.20281
Valid N (list wise)	1200	

Data presented as mean ± SD.

The mean gestational age was 25.51±8.72 weeks. Most women were in their third trimester (51.8%), while 35.5% were in the second trimester and 12.7% in the first (Figure 1).

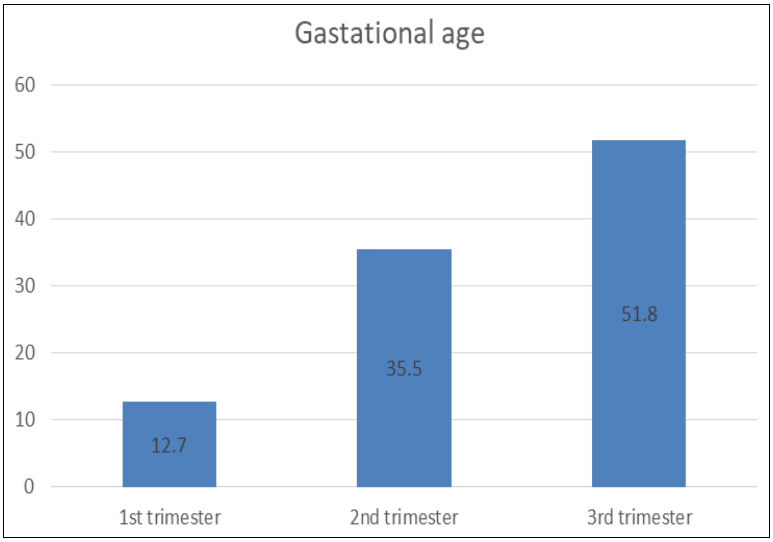

Fig 1: Showing gestational age of study participants.

In terms of gravidity, 23.6% were primigravida, 51.6% were multigravida (2-4 pregnancies), and 24.8% were grand multigravida (≥ 5 pregnancies), (Figure 2).

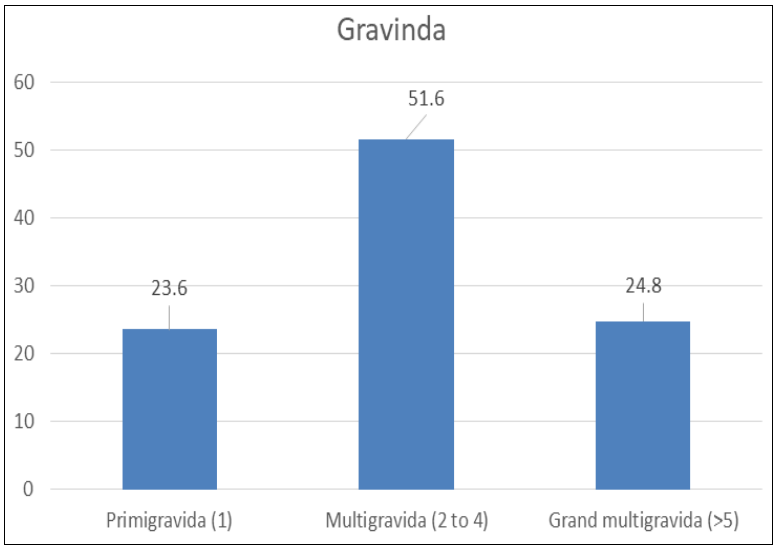

Fig 2: Showing gravidity of study participants.

Regarding thyroid status, 87.7% of participants were euthyroid, 9.3% had subclinical hypothyroidism, and 3.1% were diagnosed with overt hypothyroidism (Figure 3).

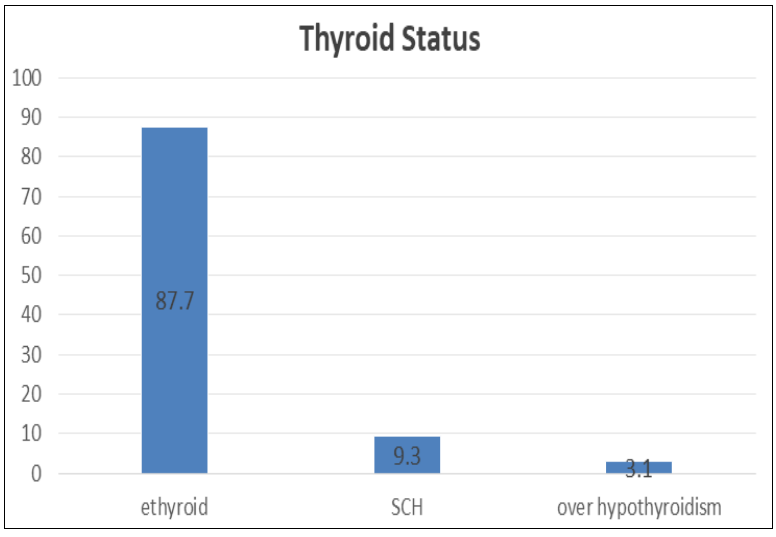

Fig 3: Thyroid status of study participants

Pearson correlation analysis demonstrated a significant positive correlation between TSH and anti-TPO antibody levels (r=0.204, p<0.001), while no significant correlation was found between anti-TPO and FT4 (r=-0.006, p=0.835), or between FT4 and TSH (r=-0.045, p=0.116). (Table no 2)

Table 2: Correlation between TSH, TPO and FT4.

Correlations	TSH	TPO	FT4
TSH	1	0.204**	-0.045
TPO	0.204**	1	-0.006
FT4	-0.045	-0.006	1

**. Correlation is significant at the 0.01 level (2-tailed).

Half of the participants (50.8%) reported one or more high-risk factors in their obstetric history. Only 2.5% had a relevant past or current medical disorder. Family history of thyroid disorders was present in 0.4% of participants, and 0.6% reported relevant drug use (Table 3). All participants had normal ultrasound findings.

Table 3: Patients' Medical history.

Variables	Yes (%)	No (%)
Past high-risk factor one or more	50.8%	49.2
Past medical history	2.5%	97.5%
Current medical disorder	2.5%	97.5%
Family history of thyroid disorder	0.4%	99.6%
Drug history	0.6%	99.4%
Ultra sound scans normal	100%	0%

Data presented as N (%).

A history of miscarriage was reported by 29.3% of the cohort. Other adverse obstetric outcomes included preterm birth (6%), intrauterine death (6.1%), neonatal death (7.5%), and congenital malformations (2.3%). IUGR was reported in 1.3% of cases. Placental abruption and postpartum hemorrhage were rare, occurring in 0.4% and 0.8% of participants, respectively. The incidence of gestational diabetes mellitus (GDM) was 2.5%, while macrosomia and PIH/pre-eclampsia were reported in 0.7% and 2.9% of previous pregnancies, respectively (Table 4).

Table 4: Past obstetrical history of 1200 patients.

History	Yes (%)	No (%)
Miscarriages	29.3%	70.8%
Congenital malformation of Fetus/New-born	2.3%	97.7%
Preterm birth (28-36 weeks)	6%	94%
IUGR	1.3%	98.7%
IUDS	6.1%	93.9%
Placenta Abruption	0.4%	99.6%
Postpartum Hemorrhage	0.8%	99.2%
NND	7.5%	92.5%
GDM	2.5%	97.5%
Macrosomia	0.7%	99.3%
PIH/PE	2.9%	97.1%

Data presented as N (%).

Discussion

This study presents a comprehensive assessment of thyroid function and obstetric outcomes among 1,200 pregnant women. The majority of participants were aged between 26-35 years, aligning with the typical reproductive age range, with a mean age of 27.45±5.15 years. Most women were in the third trimester at the time of assessment, a factor that may influence both hormonal fluctuations and obstetric complications. Our findings show that 87.7% of participants were euthyroid, while 9.3% had subclinical hypothyroidism and 3.1% had overt hypothyroidism. These figures are consistent with previous studies from South Asia and other low- to middle-income countries, which have reported subclinical hypothyroidism rates ranging from 5-12% in pregnancy. [8] The relatively high frequency of thyroid dysfunction highlights the importance of routine thyroid screening in antenatal care, particularly given the known implications of thyroid disorders for maternal and fetal health [9].

Obstetric outcomes associated with both overt and subclinical hypothyroidism have been examined in several studies; however, only a limited number have explored the contributing factors that influence adverse gestational outcomes within this population [10, 11]. A major challenge lies in the variability among population-based studies, as the thyroid axis is modulated by factors such as the population's iodine nutritional status, environmental and genetic influences, and the prevalence of autoimmune disorders. For instance, in a low-risk cohort, maternal age, blood pressure status, and smoking were found to have no significant differences between women with normal thyroid function and those with subclinical hypothyroidism.[12] Another study found no association between thyroid antibody positivity and miscarriage rates; however, it did report a significant association between maternal parity and gestational hypertension, as well as an increased risk of postpartum hemorrhage in antibody-positive women with concurrent gestational diabetes or chronic hypertension [13]. A meta-analysis concluded that Treatment of SCH with levothyroxine during pregnancy is associated with decreased risks of pregnancy loss and neonatal death [14].

Despite a high rate of euthyroidism, adverse obstetric outcomes were not uncommon in this population. Nearly half of the participants (50.8%) had one or more high-risk obstetric factors, and 29.3% had a history of miscarriage. Notably, intrauterine death (6.1%), neonatal death (7.5%), and preterm birth (6%) were recorded at slightly elevated levels compared to global averages. Although causality cannot be inferred from this cross-sectional study, the presence of thyroid dysfunction may have contributed to some of these adverse outcomes.

While there is ample statistical evidence supporting the association between hypothyroidism and recurrent miscarriages, [15] the role of a prior history of miscarriage as an independent risk factor for pregnancy loss in hypothyroid women remains underexplored. A retrospective study found no significant difference in the likelihood of achieving subsequent pregnancies between women with borderline hypothyroidism and those who were euthyroid (55.4% vs 51.3%). However, the rate of pregnancy loss before 22 weeks of gestation was higher among women with borderline-subclinical hypothyroidism compared to euthyroid women (29.0% vs 17.9%), although the difference did not reach statistical significance (P=0.16) [16].

A study conducted in Bangladesh did not find a statistically significant association between elevated TSH levels and first-trimester pregnancy loss [17]. In this cohort, most women had been diagnosed with hypothyroidism prior to conception and were already receiving levothyroxine therapy. Although preconception TSH levels were not available for the majority of participants, those who presented during the second trimester appeared to have a higher likelihood of pregnancy loss compared to those who presented in the third trimester.

The significant positive correlation observed between TSH and anti-TPO antibody levels (r=0.204, p<0.001) is consistent with the autoimmune nature of thyroid dysfunction, particularly Hashimoto's thyroiditis. However, the lack of significant correlation between anti-TPO and FT4 levels, as well as between

FT4 and TSH, may reflect the homeostatic compensation by the hypothalamic-pituitary-thyroid axis, especially in subclinical stages [18].

Interestingly, the incidence of gestational diabetes mellitus (2.5%) and preeclampsia/PIH (2.9%) was relatively low in this cohort. While some studies have proposed a link between hypothyroidism and increased risk of GDM or hypertensive disorders of pregnancy, this association was not prominent in our population, possibly due to the high rate of euthyroid status and the overall young age of participants. The presence of a family history of thyroid disease (0.4%) and relevant drug use (0.6%) was minimal, which may suggest either underreporting or a low burden of recognized risk factors. Given the significant proportion of women with anti-TPO positivity, further prospective studies are needed to evaluate long-term maternal and neonatal outcomes, particularly in euthyroid women with thyroid autoimmunity. A recent meta-analysis has shown that subclinical hypothyroidism with positive anti-thyroid antibodies significantly increases the GDM risk [19]. In another study, the incidence of thyroid dysfunction was found similar between GDM and non-GDM women [20]. The existence of both endocrine disorders has a higher effect on adverse pregnancy-related outcomes compared to either comorbidity alone [21].

Ultrasound findings were uniformly normal in this cohort, which may reflect timely antenatal screening and care, as 76.3% of participants were booked. This underscores the importance of early and regular prenatal visits, not only for monitoring fetal growth and anomalies but also for identifying and managing endocrine disturbances. The findings regarding gravidity also deserve attention. A significant number of women were multigravida or grand multigravida, with a non-negligible burden of adverse outcomes such as miscarriage and neonatal complications. These outcomes, coupled with the presence of thyroid dysfunction, warrant close surveillance and possibly targeted screening in multiparous women.

Strengths and Limitations

A key strength of this study is the large sample size and the inclusion of detailed thyroid, anthropometric, and obstetric data. However, its cross-sectional design limits the ability to establish temporal or causal relationships. Additionally, data on iodine status, which may significantly influence thyroid function, were not available. The low reported rates of family history and drug use may also suggest recall bias or underreporting.

Conclusion

This study reinforces the high prevalence of thyroid dysfunction, particularly subclinical hypothyroidism, among pregnant women and its association with adverse obstetric outcomes. Routine antenatal screening for thyroid function, particularly in women with high-risk obstetric profiles or autoimmune markers, may be warranted to mitigate potential complications. Further prospective studies are needed to clarify the impact of thyroid autoimmunity in euthyroid pregnant women and to guide management strategies in resource-limited settings.

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