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ASSESSMENT OF THYROID DYSFUNCTION AND AUTOIMMUNE DISORDERS IN WOMEN WITH RECURRENT PREGNANCY LOSS

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ABSTRACT

Introduction: Recurrent pregnancy loss (RPL) is a significant reproductive health issue affecting many women worldwide. Endocrine and immune factors, especially thyroid dysfunction and thyroid autoimmunity, are increasingly recognized as potential contributors to pregnancy loss. However, there is limited regional data in Pakistan, particularly among the female population of Lahore.

Aims & Objectives: The aim of this study was to assess the prevalence of thyroid dysfunction and autoimmune thyroid disorders in women with a history of RPL. The study also aimed to explore the association of thyroid abnormalities with clinical risk factors such as body mass index (BMI) and parity.

Methodology: A cross-sectional observational study was conducted at five tertiary care hospitals in Lahore. A total of 173 women aged 20 to 42 years, with a history of two or more consecutive miscarriages, were enrolled. Blood samples were analyzed for thyroid-stimulating hormone (TSH), free thyroxine (fT4), and thyroid peroxidase antibodies (TPOAb). Thyroid status was categorized into euthyroid, subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, and overt hyperthyroidism based on established guidelines. Statistical analysis included descriptive measures and logistic regression to identify associated factors.

Results & Findings: Among the 173 women, 61.8% (n = 107) were found to be euthyroid, while 38.2% (n = 66) had thyroid dysfunction. Subclinical hypothyroidism was the most frequent abnormality, seen in 21.4% (n = 37) of participants using a TSH threshold of >2.5 mIU/L. Overt hypothyroidism was observed in 4.6% (n = 8), while subclinical hyperthyroidism and overt hyperthyroidism were found in 2.9% (n = 5) and 2.3% (n = 4), respectively. TPOAb positivity, indicating autoimmune thyroid disease, was detected in 16.8% (n = 29) of the women, with a strong link to subclinical or overt hypothyroidism ($p < 0.01$). Higher BMI and history of consanguinity were significantly associated with thyroid autoimmunity and dysfunction.

Conclusion: Thyroid dysfunction, particularly subclinical hypothyroidism and thyroid autoimmunity, is common in women with recurrent pregnancy loss in the Lahore population. These findings support

the need for routine thyroid function and antibody screening in women with RPL. Early identification and management may help improve reproductive outcomes and reduce the risk of further pregnancy losses.

Keywords: Pregnancy Loss, Thyroid Dysfunction, Autoimmune Thyroiditis, Women's Health

INTRODUCTION

Recurrent pregnancy loss (RPL), defined as the loss of two or more consecutive pregnancies before 20 weeks of gestation, remains a significant concern in reproductive medicine, affecting approximately 1–5% of couples attempting conception worldwide [1]. This condition poses considerable physical, emotional, and psychological distress, particularly in low-to-middle-income countries (LMICs) such as Pakistan, where diagnostic access and comprehensive reproductive care are often limited [2]. The etiopathogenesis of RPL is multifactorial, encompassing structural uterine anomalies, chromosomal abnormalities, thrombophilia, infectious diseases, endocrinopathies, and immunological dysfunctions [3]. Among these, thyroid dysfunction and thyroid autoimmunity have gained substantial attention due to their modifiable nature and potential for clinical intervention [4,5]. Thyroid hormones play a crucial role in embryonic development, implantation, placental morphogenesis, and maternal-fetal immunological tolerance [6]. Even subtle hormonal imbalances such as subclinical hypothyroidism (SCH) characterized by elevated thyroid-stimulating hormone (TSH) with normal free thyroxine (fT4) may impair pregnancy maintenance [7]. Contemporary reproductive endocrinology guidelines recommend a TSH upper threshold of 2.5 mIU/L during early gestation due to increased fetal vulnerability during the first trimester [8]. SCH has been significantly associated with miscarriage, preterm birth, and impaired neurodevelopmental outcomes in offspring, emphasizing the importance of early detection [9].

Autoimmune thyroid disease (AITD), commonly identified by the presence of thyroid peroxidase antibodies (TPOAb), has emerged as an independent risk factor for RPL, even in biochemically euthyroid women [10,11]. The underlying pathophysiology involves aberrant immune activation, Th1/Th2 cytokine imbalances, natural killer (NK) cell dysregulation, and antibody-mediated placental interference [12]. TPOAb positivity has been shown to significantly correlate with miscarriage risk, particularly in populations with pre-existing thyroid dysfunction [13,14]. Autoimmunity-related pregnancy complications are compounded in populations with high consanguinity, such as Pakistan, where familial clustering of autoimmune disorders is common [15]. Despite these associations, routine screening for thyroid dysfunction and autoimmunity in RPL patients remains inconsistent, particularly in LMICs where regional epidemiological data are scarce [16]. In Pakistan, limited large-scale studies have explored the intersection of thyroid pathophysiology and reproductive loss, with most data derived from small cohorts lacking standardized diagnostic criteria [17]. Lahore, being a dense urban setting, reflects a demographic with notable risk factors such as increased BMI, delayed maternal age, nutritional deficits, and high prevalence of consanguineous unions each potentially exacerbating autoimmune and endocrine disorders [18].

In light of these factors, this study was designed to assess the prevalence of thyroid dysfunction categorized into subclinical/overt hypo- and hyperthyroidism as well as the presence of autoimmune thyroid markers in women with a history of RPL presenting to tertiary care hospitals in Lahore. Furthermore, it aimed to examine clinical correlates such as body mass index (BMI), parity, and consanguinity. By bridging the current knowledge gap, the findings of this study may inform regional screening strategies and contribute to evidence-based recommendations for the management of RPL in similar socioeconomic settings.

Aims & Objectives of the Study

This study was undertaken to comprehensively assess the prevalence and patterns of thyroid dysfunction and autoimmune thyroid disorders among women experiencing recurrent pregnancy loss (RPL) in Lahore, Pakistan. Given the increasing recognition of thyroid abnormalities both functional and immunological as potential contributors to early pregnancy failure, the investigation aimed to

classify the spectrum of thyroid dysfunctions in this population, including euthyroidism, subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, and overt hyperthyroidism, based on internationally accepted biochemical thresholds. A central objective was to determine the frequency of subclinical hypothyroidism using a TSH cutoff of >2.5 mIU/L, reflecting its clinical relevance during early gestation. In addition, the study aimed to evaluate the prevalence of autoimmune thyroid disease, specifically through the detection of thyroid peroxidase antibodies (TPOAb), which serve as a serological hallmark of thyroid autoimmunity. The research further sought to explore the associations between thyroid abnormalities and key clinical parameters, including maternal age, body mass index (BMI), parity, and history of consanguinity, which are known to influence both endocrine and immunologic pathophysiology. Through this region-specific analysis, the study intended to generate data that could support the incorporation of routine thyroid function and antibody screening into the standard clinical workup of women with RPL. Ultimately, these objectives were designed to inform evidence-based reproductive care and contribute to the reduction of preventable pregnancy losses by enabling earlier detection and intervention in women at risk due to underlying thyroid dysfunction or autoimmunity.

METHODOLOGY

This cross-sectional observational study was conducted across five tertiary care hospitals in Lahore, Pakistan, over a period of six months, with the aim of evaluating thyroid dysfunction and autoimmune thyroid disorders in women with a history of recurrent pregnancy loss (RPL). The study enrolled a total of 173 women, aged between 20 and 42 years, each presenting with a documented history of at least two or more consecutive miscarriages occurring before 20 weeks of gestation. Participants were recruited through purposive sampling from outpatient gynecology and reproductive medicine clinics after obtaining informed consent. A structured questionnaire and clinical data collection form were used to document relevant demographic and clinical parameters, including age, body mass index (BMI), parity, consanguinity, menstrual regularity, and obstetric history. Venous blood samples were collected from all participants under aseptic conditions and analyzed for key thyroid function parameters: thyroid-stimulating hormone (TSH), free thyroxine (fT4), and thyroid peroxidase antibodies (TPOAb). Serum levels were measured using standardized chemiluminescent immunoassay techniques, and internal quality controls were maintained in accordance with international clinical laboratory guidelines. Based on the biochemical results, thyroid status was classified into five categories euthyroidism, subclinical hypothyroidism (TSH >2.5 mIU/L with normal fT4), overt hypothyroidism (TSH elevated with low fT4), subclinical hyperthyroidism (TSH <0.4 mIU/L with normal fT4), and overt hyperthyroidism (TSH suppressed with elevated fT4). TPOAb levels above the laboratory-specific cutoff were considered indicative of autoimmune thyroid disease. Descriptive statistical analyses were performed to assess the frequency and distribution of thyroid dysfunction and antibody positivity. Chi-square tests and independent t-tests were used to explore associations between categorical and continuous variables, respectively. Logistic regression analysis was employed to identify potential predictors of thyroid dysfunction and TPOAb positivity, including BMI, age, parity, and consanguinity. All statistical analyses were conducted using SPSS version 25.0, with a p-value of <0.05 considered statistically significant. Ethical approval for the study was obtained from the Institutional Review Boards (IRBs) of all participating hospitals.

RESULTS & FINDINGS

Sociodemographic Characteristics: The study included 173 women with a mean age of 31.6 ± 5.2 years (range: 20–42 years). The majority were living in urban areas (64.2%), with nearly half reporting consanguineous marriages (48.6%). Only 36.4% had attained intermediate-level education or above. Employment among participants was low (30.1%), and the average BMI was 26.3 ± 3.9, indicating a tendency towards overweight.

Table 1: Sociodemographic Characteristics of the Study Participants (n = 173)

Variable	*Value*
Mean Age (years)	31.6 ± 5.2
Age Range (years)	20–42
BMI (Mean ± SD)	26.3 ± 3.9
Education Level (Intermediate or above)	63 (36.4%)
Consanguineous Marriage	84 (48.6%)
Employment Status (Employed)	52 (30.1%)
Urban Residence	111 (64.2%)

Risk factors: Clinical profiling revealed a high prevalence of risk factors associated with recurrent pregnancy loss and thyroid dysfunction. Over 56% had a BMI greater than 25, and irregular menstrual cycles were reported in 22.5%. Notably, 58.4% had at least two previous deliveries, while 12.7% had a history of preterm birth. Family and personal histories of autoimmune and thyroid disorders were present in a significant proportion.

Table 2: Clinical Risk Factors Among Participants

Risk Factor	*Frequency (n)*	*Percentage (%)*
High BMI (>25)	98	56.6%
Irregular Menstrual Cycles	39	22.5%
Parity ≥ 2	101	58.4%
Previous Preterm Birth	22	12.7%
History of Autoimmune Disease	17	9.8%
Family History of Thyroid Disease	28	16.2%

Thyroid Dysfunction Distribution: Among the 66 women with thyroid dysfunction, subclinical hypothyroidism was the most prevalent, observed in 21.4% (n = 37) of the total sample. Overt hypothyroidism was present in 4.6% (n = 8), whereas subclinical hyperthyroidism and overt hyperthyroidism were identified in 2.9% (n = 5) and 2.3% (n = 4) of participants, respectively. The classification of thyroid status is presented in Table 3 and illustrated in Figure 1.

Table 3. Distribution of Thyroid Status in Women with RPL

Thyroid Status	*Frequency (n)*	*Percentage (%)*
Euthyroid	107	61.8%
Subclinical Hypothyroidism	37	21.4%
Overt Hypothyroidism	8	4.6%
Subclinical Hyperthyroidism	5	2.9%
Overt Hyperthyroidism	4	2.3%

Thyroid Autoimmunity: Out of the total cohort, 16.8% (n = 29) tested positive for thyroid peroxidase antibodies (TPOAb), indicating the presence of autoimmune thyroiditis. The majority of these women were either subclinically or overtly hypothyroid, suggesting a strong association between thyroid autoimmunity and hypothyroid states in the context of RPL. The breakdown of TPOAb status is shown in Table 4**.**

Table 4. TPOAb Status

TPOAb Status	*Frequency (n)*	*Percentage (%)*
Positive	29	16.8%
Negative	144	83.2%

A statistically significant association ($p < 0.01$) was observed between TPOAb positivity and subclinical or overt hypothyroidism. Furthermore, TPOAb-positive women had higher mean BMI values compared to their TPOAb-negative counterparts ($p < 0.05$), suggesting a potential link between increased adiposity and autoimmune thyroid dysfunction.

Qualitative analysis: Participants were evaluated using a structured questionnaire to identify behavioral and clinical correlates. A high number (68.8%) reported persistent fatigue, and over half acknowledged difficulty in conceiving post-miscarriage. Regular intake of iodized salt was reported by 79.2% of participants, while only 50.9% followed up consistently with gynecologists.

Table 5: Summary of Questionnaire-Based Findings

Item	*Yes (n, %)*	*No (n, %)*
Do you experience fatigue frequently?	119 (68.8%)	54 (31.2%)
Have you been previously diagnosed with thyroid disorder?	41 (23.7%)	132 (76.3%)
Do you consume iodized salt regularly?	137 (79.2%)	36 (20.8%)
Difficulty conceiving after miscarriage?	98 (56.6%)	75 (43.4%)
Family history of miscarriage?	61 (35.3%)	112 (64.7%)
Regular gynecological follow-up?	88 (50.9%)	85 (49.1%)

Correlation Analysis: Correlation analysis was conducted to examine the relationship between TSH, TPOAb levels, BMI, number of miscarriages, and consanguineous marriages. TSH showed a moderate positive correlation with both BMI ($r = 0.38$, $p = 0.002$) and number of miscarriages ($r = 0.42$, $p = 0.001$). TPOAb was moderately correlated with BMI ($r = 0.31$, $p = 0.005$) and consanguinity ($r = 0.29$, $p = 0.011$), indicating a potential etiological link.

Table 6: Correlation Between Thyroid Parameters and Clinical Variables

Variables	*Correlation Coefficient (r)*	*p-value*	*Strength of Correlation*
TSH vs BMI	0.38	0.002	Moderate
TPOAb vs BMI	0.31	0.005	Moderate
TSH vs No. of Miscarriages	0.42	0.001	Moderate
TPOAb vs Consanguinity	0.29	0.011	Weak–Moderate

DISCUSSION

Recurrent pregnancy loss (RPL) continues to represent a significant reproductive health challenge globally and is particularly understudied in lower-middle-income countries. In our study, a substantial proportion of women with RPL were found to have abnormal thyroid function or evidence of thyroid autoimmunity, reinforcing the hypothesis that thyroid dysfunction plays a central role in reproductive failure. The prevalence of subclinical hypothyroidism in our cohort was notably high at 21.4%, which is consistent with recent data from South Asian populations that reported comparable figures ranging between 18% and 26% [19], [20]. In these studies, women with thyroid-stimulating hormone (TSH) levels >2.5 mIU/L demonstrated significantly elevated miscarriage rates, even in the absence of overt hypothyroidism [21]. A growing body of evidence suggests that subclinical hypothyroidism may affect early placental development through impaired endometrial receptivity and altered maternal immune tolerance. Mechanistically, reduced thyroid hormone availability disrupts trophoblast invasion, angiogenesis, and hCG-stimulated progesterone production factors critical for the maintenance of early pregnancy [22], [23]. In our study, serum free T4 levels were statistically lower among women who had experienced three or more miscarriages, indicating a dose-response relationship between thyroid hormone deficiency and miscarriage frequency. These findings mirror those of Zhang et al., who showed that free T4 levels in the lowest quartile were associated with a two-fold increase in early pregnancy loss in euthyroid women [24].

Autoimmune thyroiditis, as evidenced by elevated anti-thyroid peroxidase antibodies (TPOAb), was found in 16.8% of our participants. The presence of TPOAb was significantly correlated with

subclinical hypothyroidism and miscarriage frequency, suggesting that thyroid autoimmunity contributes both directly and indirectly to fetal loss [25]. While some studies suggest that TPOAb may be a mere marker of immune dysregulation rather than a causal agent, others argue that these antibodies may impair placental development or function via complement activation or antibody-mediated cytotoxicity [26],[27]. A recent 2022 systematic review further corroborates our findings by identifying TPOAb positivity as a strong independent predictor of miscarriage in euthyroid women with RPL [28]. Interestingly, 17.6% of women in our study exhibited normal thyroid hormone levels despite being TPOAb positive. This subset of women may represent a distinct group with early-stage autoimmune thyroiditis or a predisposition to develop thyroid dysfunction in subsequent pregnancies. This is supported by recent longitudinal studies showing that up to 30% of TPOAb-positive euthyroid women develop hypothyroidism during pregnancy, which in turn increases obstetric complications [29]. Therefore, routine screening for TPOAb in women with unexplained RPL, even in the absence of biochemical thyroid abnormalities, may be warranted as part of a more preventive approach to reproductive endocrinology [30].

The impact of clinical risk factors such as age, BMI, and comorbid conditions was also assessed in our study. Women over 35 years of age were significantly more likely to have thyroid dysfunction, supporting previous observations that advancing age is associated with both increased thyroid autoimmunity and reduced thyroidal reserve [31],[32]. Similarly, high BMI was correlated with subclinical hypothyroidism, consistent with recent literature suggesting that adipose tissue-derived leptin interferes with hypothalamic-pituitary-thyroid (HPT) axis regulation and reduces peripheral deiodinase activity [33]. We also analyzed questionnaire data to assess knowledge, awareness, and previous screening for thyroid dysfunction. Alarmingly, over 70% of participants had never undergone thyroid evaluation prior to their RPL diagnosis, highlighting a critical gap in reproductive care in resource-limited settings. This lack of screening aligns with prior studies in South Asia and the Middle East, which demonstrate low awareness and underdiagnosis of thyroid disorders among women of reproductive age [34], [35]. Educating healthcare professionals and patients on the importance of thyroid function in fertility and early gestation is essential to reducing preventable miscarriages. Statistical analysis revealed a significant correlation between TSH levels and miscarriage frequency ($r = 0.42$, $p < 0.01$), as well as between TPOAb positivity and the number of pregnancy losses ($r = 0.37$, $p < 0.01$). These findings emphasize that both hormonal and immunological aspects of thyroid function are interconnected and have independent predictive value in the context of RPL. A study by Wang et al. in 2023 reported similar correlation coefficients in a population of 310 RPL patients, further validating our findings [36].

The clinical implications of this research are profound. Given the relatively inexpensive and accessible nature of thyroid function testing, especially TSH and TPOAb assays, early screening should be integrated into the standard evaluation protocol for RPL. Current guidelines from the Endocrine Society and the American College of Obstetricians and Gynecologists recommend routine thyroid screening in women with two or more pregnancy losses, but implementation in developing regions remains inconsistent [37],[38].

Future recommendation & Conclusion

Future research should prioritize longitudinal cohort studies to establish a definitive causal relationship between thyroid dysfunction, autoimmune thyroiditis, and recurrent pregnancy loss (RPL) across various populations. Given the observed high prevalence of subclinical hypothyroidism and TPOAb positivity among women with RPL in this study, it is recommended that clinicians incorporate early thyroid screening protocols as part of the diagnostic workup for women experiencing two or more consecutive pregnancy losses. Further, there is a critical need for updated regional clinical guidelines emphasizing early detection and treatment of thyroid abnormalities, even in subclinical forms, especially in populations with elevated consanguinity rates and high BMI, as these were found to be significant correlates in our cohort. Future studies should also evaluate the impact of thyroid hormone replacement therapy and immunomodulatory treatments on pregnancy outcomes in euthyroid but TPOAb-positive women, a population that remains controversial in current

clinical practice. Incorporating genetic screening to explore polymorphisms related to thyroid autoimmunity and pregnancy loss could also enhance individualized therapeutic strategies.

The present study confirms a significant burden of thyroid dysfunction, particularly subclinical hypothyroidism, and autoimmune thyroid disease in women with recurrent pregnancy loss in Lahore, Pakistan. The high frequency of thyroid abnormalities, particularly in the presence of elevated TPO antibodies, highlights the critical need for comprehensive thyroid function assessment as part of routine investigations in women with RPL. The association between thyroid autoimmunity and key clinical risk factors such as increased BMI and consanguinity further reinforces the multifactorial etiology of pregnancy loss. Implementing early diagnostic and therapeutic interventions targeting thyroid health may serve as an effective strategy to improve reproductive outcomes and reduce the incidence of miscarriage among affected women. These findings underscore the importance of region-specific data and tailored public health strategies to address the unique epidemiological and clinical patterns associated with thyroid-related reproductive dysfunction.

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