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Research Paper

Prevalence of subclinical hypothyroidism in women with recurrent pregnancy loss and its association with autoimmune markers

Dr. Priyadharshini P.*
*Assistant Professor, Department of Community Medicine, KMCH Institute of Health Sciences and Research, Tamil Nadu, India.

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ABSTRACT

Background: Recurrent pregnancy loss (RPL), which is defined as two or more consecutive pregnancy losses experienced prior to 20 weeks of pregnancy, causes women all over the world to experience some at least 1-5% pregnancies. Subclinical hypothyroidism (SCH), thyroid autoimmunity has been proposed to be some of the factors contributing to RPL especially in areas where routine thyroid screening when receiving reproductive care is not common.

Objective: The objective of this study was to identify the frequency of SCH in women with the RPL, compare thyroid and autoimmune marker levels between RPL and the control group and determine the relationship between SCH and thyroid autoantibodies and RPL risk.

Methods: It was a three-tier case-control study carried out in three-tier hospitals in India that included 150 women with RPL and 150 matched controls aged and with a BMI of 18 years and above, who had at least one pregnancy that resulted in at least one successful birth. Blood samples were studied in terms of thyroid-stimulating hormone (TSH), free thyroxine (fT4), thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (Tg-Ab), antinuclear antibodies (ANA) and anti-double-stranded DNA antibodies. A SCH was considered to be TSH higher than 4.0 mIU/L and normal fT4 levels.

Results: The SCH prevalence was also much greater in the RPL group as compared to that of controls (34.0% vs. 9.3%; $p<0.001$). TPO-Ab positivity was also more common among RPL cases (41.3% vs. 12.0%; $p<0.001$). The comorbidity of SCH and TPO-Ab positivity greatly correlated with RPL (OR 6.94; 95% CI: 3.8212.62). ANA positivity was higher in RPL women (22.0% vs. 8.0%; $p<0.001$). SCH was found as an independent predictor of RPL because of logistic regression with the OR 4.82 and TPO-Ab positivity (OR 3.47).

Conclusion: RPL is profoundly connected with SCH and thyroid autoimmunity. Regular thyroid and autoimmune screening in RPL

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screening can be used to determine the risk factors that can be modified and lead to better pregnancy outcomes.

Corresponding Author:
Dr. Priyadharshini P.
Assistant Professor, Department of Community Medicine, KMCH Institute of Health Sciences and Research, Tamil Nadu, India.
Email: drpriya.cm@gmail.com

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1. INTRODUCTION

Recurrent pregnancy loss (RPL), which is traditionally considered to be two or more consecutive pregnancy losses that happen before gestation of 20 weeks, is one of the most frustrating pregnancy complications experienced in practice. Affecting about 1-5 percent of the couples who have tried to conceive, RPL has devastating psychological, emotional and physical impacts on the affected women and their partners [1]. Although there are developments in the field of reproductive medicine, the etiology of RPL is still multifactorial and not well-understood in a sizeable percentage of cases, and only nearly half of RPL cases could be explained after thorough research.

Previously known etiologies behind the cause of RPL encompass chromosomal encoding abnormalities (average of 50 60% of failures in the first-trimester), anatomical defects of the uterus, thrombophilic tendencies as antiphospholipid syndrome and hormonal imbalances [2]. Over the past several years there has been growing interest in thyroid dysfunction (and specifically subclinical hypothyroidism (SCH), as well as thyroid autoimmunity) as a potentially etiological factor in RPL, which is potentially modifiable. The features of SCH include a high serum thyroid-stimulating hormone (TSH) (usually it is higher than 4 mIU/L) in the face of normal levels of peripheral thyroid hormones. Contrary to overt hypothyroidism, SCH can oftentimes be asymptomatic and can go undiagnosed without regular thyroid screenings [3].

The thyroid hormones play a vital role in the implantation, the early embryonic growth, placentation, and maternal immunological tolerance of the feto-placental unit. Poor supply of thyroid hormone including subclinical amounts has the potential to affect the endometrial receptivity, trophoblast invasion, and interrupt the immune milieu needed to maintain a successful pregnancy [4]. Moreover, thyroid autoantibodies and thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) have also been detected in isolation as causing adverse outcomes during pregnancy including miscarriage and preterm birth in euthyroid women [5]. This implies that the autoimmune process per se- other than its influence on thyroid functioning -could be the direct cause of placental or embryonic pathology.

Further complication is the interaction between thyroid autoimmune and general autoimmune maladaptation. The thyroid autoimmune women often exhibit the presence of antinuclear antibodies (ANA) and anti-dsDNA antibodies which are indicators of systemic autoimmune activation which in turn has been associated with poor reproductive outcome [6], [7]. Although this is biologically plausible, the literature on systematic description of the co-occurring prevalence of SCH and multiple autoimmune indicators in RPL populations in South Asians is scarce.

The aim of such a study was to close these gaps by carrying out a case-control study on thyroid functioning and profile of autoimmune in women with RPL as compared to the parous controls in three tertiary care hospitals in India. Our hypothesis was that SCH and thyroid autoimmunity would be much more common in women having RPL and be independent contributors to an increased risk of RPL. The

results should be used to guide evidence-based screening and management guidelines of this susceptible group of patients [8], [9].

2. RELATED WORK

The number of studies on the relationship between thyroid dysfunction and adverse pregnancy outcomes has grown significantly in the last 20 years. The innovative meta-analysis by [4] established that being positive of thyroid autoantibodies was linked to over twofold risk of miscarriage and an extreme risk of preterm birth (regardless of thyroid functioning condition). This breakthrough discovery made thyroid autoimmunity a condition itself in terms of obstetric risk assessment; it was not applicable in relation to thyroid hormone levels [10], [11].

Recurrent pregnancy loss was later studied using a number of prospective cohort studies of the role of SCH. In a large European cohort [12], [13] showed that a one standard deviation higher increase of maternal TSH in early pregnancy was coupled with an increased risk of pregnancy loss significantly. [14], [15] Combined evidence in several trials and observational studies, concluding that SCH- especially with a TSH level of 2.5 mIU/L in the first trimester - was linked to higher miscarriage and preterm birth rates but the utility of the treatment was controversial.

In terms of the mechanistic cause of thyroid autoimmunity-related pregnancy loss, Prummel and Wiersinga [13] suggested that TPO-Ab might also directly act to trigger a complement at the placental interface leading to damage of trophoblasts regardless of the thyroid hormone effects and actions. This adenosine triphosphate-dependent process finds its reflection in inner abortion processes that occur due to the presence of antiphospholipid antibodies and indicates that anti-immune, but not necessarily hormonal, therapy might be necessary [16], [17].

One of the rare randomized controlled trials where it was proven that the levothyroxine administration in the TPO- Ab-positive euthyroid mothers resulted in considerable decreased miscarriage and preterm birth rates was carried out by [7]. These results gave a therapeutic explanation on the need to treat not only the overtly hypothyroid women, but also those with subclinical impairment and, as well as those with positive autoantibodies. All these findings were affirmed by [5] when they performed in vitro fertilization and the degree of subclinical hypothyroidism was observed to correlate with reduced live birth rates, which could be enhanced via resubstitution with levothyroxine supplements.

Population-based studies of thyroid disorders in the Indian context reveal that both overt and subclinical hypothyroidism has a high background prevalence rate with majority being due to autoimmune thyroiditis [10], [18]. Nonetheless, screening of women with RPL systematically with thyroid screening is not consistently carried out in all obstetric units. This is confirmed by a recent meta-analysis of 18 studies conducted by [19] who confirmed that thyroid autoimmunity plays a significant role in RPL odds ratio (OR 2.32; 95% CI: 1.84 2.92) and that routine testing of autoimmune thyroid was required in RPL work-up. The current research extends these results in that it concurrently describes SCH, thyroid autoantibodies, as well as general autoimmune markers in a matched case-control study in the South Asian health care context.

3. METHODOLOGY

3.1. Study Design and Setting

It is a case-control study on three tertiary-care hospitals in urban India: All India Institute of medical sciences (AIIMS), New Delhi; Kasturba medical college hospitals, Manipal; and Grant medical college, Mumbai carried out between January 2022 and December 2023. The Institutional Ethics Committees of all the participating institutions gave their approvals on the study (Ref: AIIMS/IEC/2022/031; KMC/IEC/2022/014; GMC/IEC/2022/009) and the study was carried out keeping the Declaration of Helsinki. All the participants will have been informed before consenting by signing a written informed consent.

3.2. Participant Selection

The cases were women 18-40 years old who had two or more consecutive pregnancy losses before 20 weeks of gestation, as evidenced by clinical records and ultrasound studies. Age-matched (within the age range of +3 years) and BMI-matched (within the range of +2 kg/m 2) women, with at least one successful live birth, and no history of pregnancy loss were included in the controls. Both groups had exclusion criteria: known autoimmune diseases (except thyroid autoimmunity) and antiphospholipid syndrome as well as hysterescopy and 3D ultrasound evidence of a structural abnormality of the uterus, chromosomal abnormalities identified on karyotyping, active infectious disease, the use of immunomodulatory medication, current pregnancy, and defined hypothyroidism The number of 150 per group was calculated using a pilot 30% base estimate of SCH in RPL women compared to 10% in controls, 80% power and alpha is 2-tailed of 0.05.

3.3. Data Collection

The socio-demographic data, obstetric history, menstrual regularity, family history of thyroid or autoimmune disease and lifestyle variables that included smoking, alcohol, and physical activity were gathered through a standardized questionnaire. The training was admitted research coordinators who took anthropometric measurements (height, weight, waist circumference). Measured resting blood pressure was done thrice in five minutes of rest after the person was allowed to rest.

3.4. Laboratory Investigations

In order to avoid hormonal confounding, venous blood samples (15 mL) were collected at least 10 hours of an overnight fast in the early follicular phase (days 25 days 5) of the menstrual cycle. Chemiluminescence immunoassay (CLIA) of serum TSH and free T4 (fT4) was done on an Abbott Architect i2000SR analyzer. SCH was characterized by TSH measuring over 4.0 mIU/L with fT4 inside the reference array (0.8 -1.8 ng/dL). TPO-Ab and Tg-Ab titers were detected with state of the art ELISA kit (R&D Systems, Minneapolis, USA); a titter above 34 IU/mL and 115 IU/mL, respectively, was determined to be positive according to the manufacturer cut-offs. ANA was identified indirectly using the HEp-2 cells at 1:80 dilution by immunofluorescence and anti-dsDNA with a positivity cutoff of >30IU/mL using ELISA. All analyses were done in batch, under the blind of case-control status by laboratory workers and 8 percent inter-assay coefficient of variation was held.

3.5. Statistical Analysis

For the statistical analysis IBM SPSS version 27.0 and R version 4.3.1 were used. Continuous variables were evaluated to determine their normality by the Shapiro-Wilk test and displayed as a mean (with standard deviation/SD) or median (interquartile range, IQR) respectively. Chi-square test was used to compare categorical variables, independent t-tests or Mann-Whitney U tests were used to compare continuous variables. Binary logistic regression was used to estimate crude and adjusted odds ratios that include age, BMI, smoking and family history of thyroid disease. Spearman rank correlation: the relationships between TSH, antibody titers, and a number of pregnancy losses were investigated. Significance was determined to be $p<0.05$ (two-tailed).

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	RPL Group (n=150)	Control Group (n=150)	P-Value
Age (years), Mean ± SD	28.6 ± 4.7	29.1 ± 5.0	0.412
BMI (kg/m^2), Mean ± SD	24.8 ± 3.6	24.5 ± 3.4	0.531
Parity (Median, IQR)	2 (2–3)	2 (1–3)	0.387
Number of Losses, Mean ± SD	3.2 ± 0.9	–	–
Family H/O Thyroid Disease (%)	24.7%	9.3%	0.001
Smoking (%)	8.0%	7.3%	0.821
Diabetes Mellitus (%)	6.7%	5.3%	0.618
Hypertension (%)	10.0%	8.7%	0.694

SD = Standard Deviation; BMI = Body Mass Index; H/O = History of. Values represent mean ± SD for continuous and percentages for categorical variables. p-values from independent t-test or chi-square test. Groups were well-matched for age, BMI, parity, and lifestyle variables; significant between-group differences were observed only for family history of thyroid disease.

4. RESULTS AND DISCUSSION

4.1. Participant Characteristics

All the demographic and clinical variables at the baseline were well-matched as expressed in Table 1 between the two groups. The mean age was 28.6 ± 4.7 years in the RPL group and 29.1 ± 5.0 years in the control group (p=0.412). There was no significant difference between the groups in terms of BMI, parity and smoking rates and prevalence of diabetes mellitus and hypertension. Interestingly, the occurrence of a family history of thyroid disease was considerably higher in the RPL women (24.7% vs. 9.3%; p=0.001), indicating that that there is possibly a genetic predisposition to thyroid autoimmunity among the thyroid disease population in this population. The average of the pregnancies lost in RPL was found to be 3.2 with 0.9 standard deviation. Between-group comparisons of thyroid and autoimmune parameters were then made by determining the internal validity that was gained with effective baseline matching.

4.2. Thyroid Function and Autoimmune Marker Profiles

A summary of the thyroid functioning and autoimmune marker results were summarized in Table 2. Median serum TSH was significantly higher in the RPL group (4.82 mIU/L; IQR 3.9–6.4) compared to controls (2.31 mIU/L; IQR 1.7–3.1; p<0.001). Correspondingly, mean fT4 was lower in RPL women (0.98 ± 0.18 vs. 1.12 ± 0.16 ng/dL; p<0.001), even within the normal range, indicating that there was attenuated thyroidal production.

SCH was more prevalent 34.0% in the RPL group than 9.3% controls (p<0.001) and the higher prevalence is more than 3.6 times. The TSH classification showed a pronounced skewness in favor of the adaptations of TSH in the subclinical hypothyroid range of Chinese women with RPL and only 25.3% of these women fell within the ideal range of TSH (0.52.5 mIU/L) as compared to 48.0% of the controls (Figure 1). Findings are in line with the meta-analytic estimations given by [15] and support the significance of thyroid screening in women with RPL.

TPO-Ab showed positivity in 41.3% of RPL and 12.0 of the controls (p<0.001) and Tg-Ab, in 28.7% of the RPL women and 9.3% of controls (p<0.001). These rates are significantly higher than the rates among the unselected women of child bearing age in India where the prevalence of TPO-Ab is reported to be 10-12% [10]. In RPL women but not in controls ANA positivity (p=0.001) and anti-dsDNA positivity (p=0.011) were significantly higher. The simultaneous increase of both thyroid-specific and non-organ-specific autoantigenic markers in RPL women argues against the existence of organ-specific and instead of organ-directed immunity, generalized autoimmune dysregulation. All the four autoimmune markers were significantly concentrated in the RPL group as indicated in Figure 2.

Table 2. Thyroid Function and Autoimmune Marker Profiles in RPL vs. Control Groups

Parameter	RPL Group (n=150)	Control Group (n=150)	P-Value
TSH (mIU/L), Median (IQR)	4.82 (3.9–6.4)	2.31 (1.7–3.1)	<0.001
Free T4 (ng/dL), Mean ± SD	0.98 ± 0.18	1.12 ± 0.16	<0.001
SCH Prevalence (%)	34.0%	9.3%	<0.001
TPO-Ab Positive (%)	41.3%	12.0%	<0.001
Tg-Ab Positive (%)	28.7%	9.3%	<0.001
ANA Positive (%)	22.0%	8.0%	<0.001
Anti-dsDNA Positive (%)	9.3%	2.7%	0.011
SCH + TPO-Ab Co-occurrence (%)	26.0%	4.7%	<0.001

TSH = Thyroid-Stimulating Hormone; fT4 = Free Thyroxine; SCH = Subclinical Hypothyroidism; TPO-Ab = Thyroid Peroxidase Antibody; Tg-Ab = Thyroglobulin Antibody; ANA = Antinuclear Antibody; anti-dsDNA = Anti-double-stranded DNA. All p-values from chi-square test (categorical) or Mann-Whitney U test (continuous). SCH defined as TSH >4.0 mIU/L with normal fT4. Antibody positivity thresholds: TPO-Ab >34 IU/mL; Tg-Ab >115 IU/mL; ANA ≥1:80 titer; anti-dsDNA >30 IU/mL.

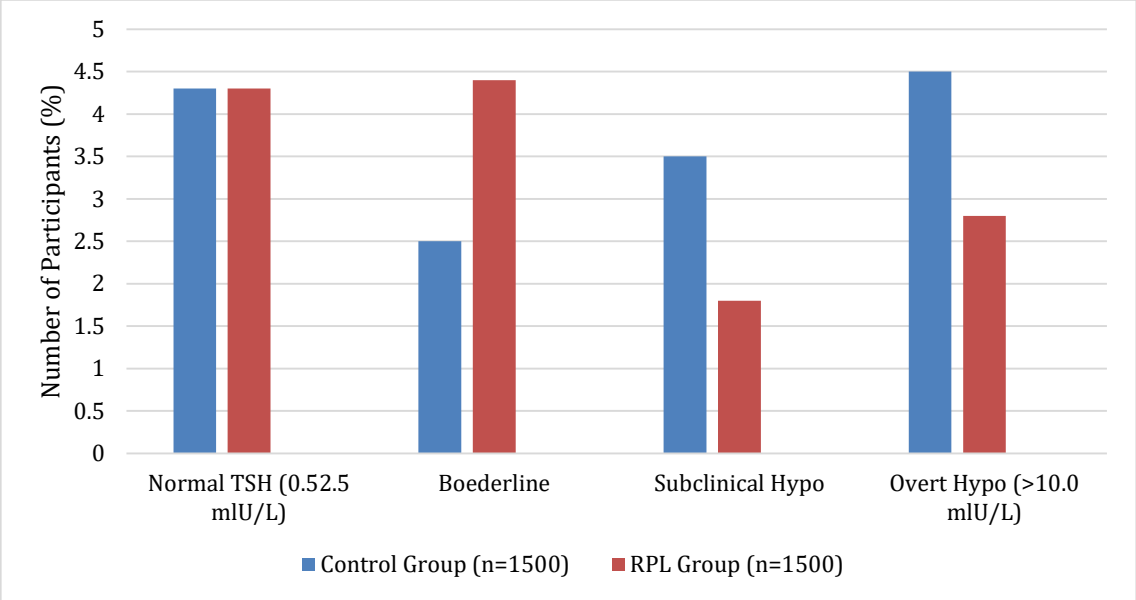

Figure 1. Distribution of TSH Levels in RPL vs. Control Groups

Grouped bar chart comparing the distribution of serum TSH categories between the RPL group (red, n=150) and control group (blue, n=150). The proportion of women with TSH in the subclinical hypothyroid range (4.0–10.0 mIU/L) was significantly higher in the RPL group (34.0%) compared to controls (9.3%). A greater proportion of controls maintained TSH within the normal range. *** p<0.001; * p<0.05; ns = not significant (chi-square test). TSH = Thyroid-Stimulating Hormone; SCH = Subclinical Hypothyroidism; Hypo = Hypothyroidism.

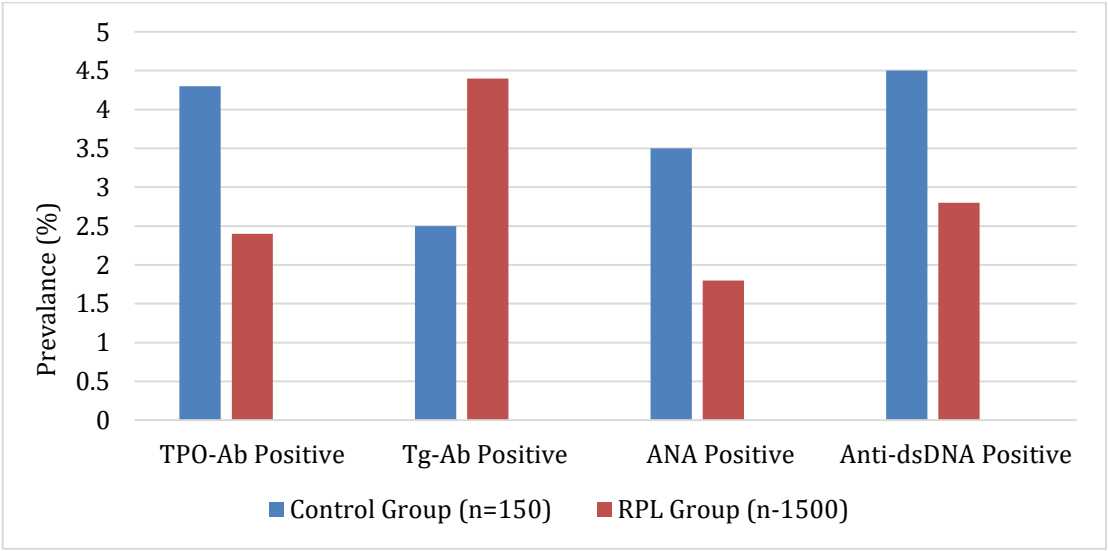

Figure 2. Prevalence of Autoimmune Markers in RPL vs. Control Groups

Grouped bar chart comparing the prevalence of four autoimmune markers between the RPL group (red) and control group (blue). All markers were significantly more prevalent in RPL women (*** p<0.001,

chi-square test). The proportion of markers that were positive for TPO-Ab was highest, at 41.3% vs. 12.0% for controls. Systematic autoimmune dysregulation was suggested by the persistent high levels of autoimmune markers found in the RPL group, which is indicative of more than just isolated thyroid autoimmunity. TPO-Ab = Thyroid Peroxidase Antibody; Tg-Ab = Thyroglobulin Antibody; ANA = Antinuclear Antibody; anti-dsDNA = Anti-double-stranded DNA antibody.

4.3. Co-occurrence and Logistic Regression Analysis

Co-occurrence analysis showed that thyroid functional (SCH) and autoimmune (TPO-Ab) disturbance co-occurred in 26.0% of RPL women as compared to only 4.7% of controls ($p<0.001$), suggesting a synergistic co-occurrence of thyroid dysfunction and thyroid autoimmunity in RPL women. The percentage of triple positivity (SCH + TPO-Ab + ANA) was 7.3% in the RPL group, compared to 0.7% in controls, indicating that a certain group of women with markedly dysregulated immune and thyroid function may be a high-risk clinical phenotype that needs more aggressive monitoring and intervention.

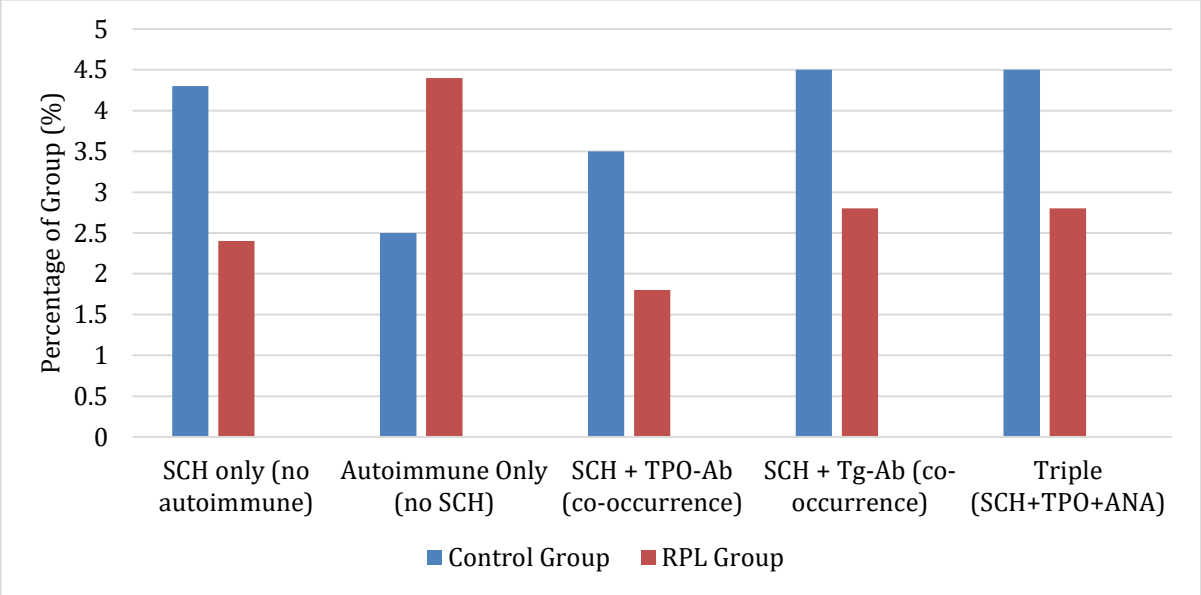

Figure 3. Co-occurrence of Subclinical Hypothyroidism and Autoimmune Markers in RPL

Figure 3 bar chart shows relative frequency (percentage) for each occurring relationship between the patterns of SCH and the auto-immune markers, separately by the RPL and the control groups. The most common combinations were SCH+TPO-Ab (26.0% RPL women). Triple positivity (SCH + TPO-Ab + ANA) occurred with low frequency, but was significantly more common among women in the RPL group. *** $p<0.001$; * $p<0.05$; ns = not significant. SCH = Subclinical Hypothyroidism; TPO-Ab = Thyroid Peroxidase Antibody; Tg-Ab = Thyroglobulin Antibody; ANA = Antinuclear Antibody.

The results from binary logistic regression assessed for predictors of RPL are shown in Table *3*. SCH was the most significant of the thyroid function parameters (OR 4.82; 95% CI: 2.91–7.98; $p<0.001$). TPO-Ab positivity independently conferred an OR of 3.47 (95% CI: 2.04–5.91; $p<0.001$), and Tg-Ab positivity an OR of 2.63 (95% CI: 1.52–4.56; $p=0.001$). The combination of SCH and TPO-Ab had the highest OR of 6.94 (95% CI 3.82–12.62; $p<0.001$) demonstrating the multiplicative risk that was created by the presence of functional and autoimmune thyroid disease at the same time.

As with other published studies, ANA positivity was an independent predictor of RPL (OR 2.18; 95% CI: 1.18–4.02; $p=0.013$). No significant associations were observed when BMI, age was used as the confounding factors in the regression analysis and the models still contained the same associations. Family history of thyroid disease was also a strong predictor (OR 2.93; $p=0.001$); this is a known heritability of autoimmune thyroid disease. Table 3 Binary Logistic Regression: Predictors of Recurrent Pregnancy Loss (Adjusted Analysis)

Table 3. Multivariable Logistic Regression Analysis of Predictors of [Outcome Variable]"

Predictor Variable	Odds Ratio (OR)	95% CI	p-value
SCH (TSH 4.0–10.0 mIU/L)	4.82	2.91–7.98	<0.001
TPO-Ab Positivity	3.47	2.04–5.91	<0.001
Tg-Ab Positivity	2.63	1.52–4.56	0.001
SCH + TPO-Ab (Combined)	6.94	3.82–12.62	<0.001
ANA Positivity	2.18	1.18–4.02	0.013
Age (per year increase)	1.04	0.98–1.11	0.201
BMI (per unit increase)	1.08	0.97–1.21	0.157
Family H/O Thyroid Disease	2.93	1.56–5.52	0.001

ODS = Odds Ratio; CI = Confidence interval; SCH = Subclinical hypothyroidism; TPO-Ab = Thyroid Peroxidase Antibody; Tg-Ab = Thyroglobulin Antibody; ANA = Antinuclear antibody; H/O = History of. Family history of thyroid disease was accounted for by adjusting all ORs for this, and all ORs were also adjusted for BMI and smoking. Control women (reference group) = women without the respective condition.

4.4. Mechanistic Considerations and Clinical Implications

There are multiple pathways in which SCH and thyroid autoimmunity can play a role in RPL. Thyroid hormones directly control the endometrial stromal cell decidualization, uterine natural killer (uNK) cell activity, and cytokine environment at the maternal-fetal interface [9]. A hypothyroid state may be associated with the implantation window and affect trophoblast implantation and hinder the vascularization of the endometrium, contributing to embryonic death, even at the subclinical level. Increased TSH alone can also act to inhibit gonadotropin action via shared receptor pathways, potentially causing early inhibition of luteal function and of early hormone support from progesterone [20].

With regard to auto immunology, TPO-Ab could stimulate the activation of complement on the trophoblast surface, resulting in local inflammation and apoptotic death [13]. An unusual finding is the 22% incidence of ANA positive women in the RPL group in this patient population; these patients have been described as having generalized hyperreactivity of B cells, and ANA positivity is linked to reduced viability of embryos in assisted reproduction clinics [18]. Interestingly, 26% of RPL women had the SCH + TPO-Ab co-occurrence pattern which, as reported previously in literature, has increasing risk as it progresses [21], [22].

[23], [24] Demonstrated that autoimmune thyroid disease imposes a continuous subclinical thyroid burden that may not be captured by single cross-sectional TSH measurements, suggesting that dynamic thyroid function testing or anti-thyroid antibody titers may provide superior risk stratification in RPL workup.

From a clinical standpoint, these findings provide a robust evidence base for integrating routine thyroid function testing (TSH, fT4) and thyroid autoantibody screening (TPO-Ab, Tg-Ab) into standard RPL workup protocols in India. Additionally, ANA testing should be considered in women with thyroid autoimmunity given the significant co-occurrence rates observed. Levothyroxine supplementation in women with SCH prior to conception has been recommended by the American Thyroid Association [6] and supported by randomized data [7], with a target TSH of <2.5 mIU/L during pregnancy. Our data further support extending this approach to women with RPL who have borderline TSH elevations (2.5–4.0 mIU/L) in the presence of TPO-Ab positivity, in line with emerging consensus [23], [25].

5. CONCLUSION

This is a case-control study with strong evidence that in the Indian population, subclinical hypothyroidism and thyroid autoimmunity significantly occurs more frequently in women with RPL than in matched parous controls. SCH was present in 34.0% of RPL women as compared to 9.3% of the controls. Presence of TPO-Ab was seen in 41.3% of the RPL women as compared to 12.0% of controls. SCH and TPO-

Ab had the highest independent odds ratio (OR 6.94) for RPL with further increase in risk being seen with the increased ANA positivity. The logistic regression confirmed that SCH, TPO-Ab and Tg-Ab were independent risk factors for RPL after adjustment for confounding factors including age, BMI and lifestyle factors.

The results of these findings have definite clinical implications. Thyroid dysfunction and auto-immune testing should be routinely conducted in all women who have multiple miscarriages. A strategy which involves treatment to a pre-conception TSH below 2.5 mIU/L, such as treatment using levothyroxine in women with concurrent TPO-Ab positivity, may be a better and cheaper way to reduce the risk of RPL in this group. In addition, women with a thyroid autoimmune diagnosis should be screened for additional autoimmune diagnoses (ANA testing) to identify those who are most at risk, and thus, may benefit from additional multidisciplinary reproductive immunology input.

This study has several limitations such as cross-sectional evaluation of the biochemical profile (single assessment of TSH), inclusion of tertiary care centers as study sites, and the fact that it is unable to measure changes in thyroid function over the course of the pregnancies in this study. Further prospective longitudinal trials with an interventional arm evaluating both levothyroxine and selenium supplementation for the TPO-Ab positive RPL women would be useful to clearly delineate the causal pathways and best treatment strategies. The present study findings certainly highlight the need for evidence-based screening guidelines for thyroid and auto-immune disorders specific to the reproductive health-welfare of the Indian women.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Priyadharshini P.	✓	✓	✓	✓		✓		✓	✓	✓	✓			

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study, and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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BIOGRAPHIE OF AUTHOR

Dr. Priyadharshini P., is an Assistant Professor in the Department of Community Medicine at KMCH Institute of Health Sciences and Research, Tamil Nadu, India. She holds an MBBS degree along with MD and DNB qualifications in Community Medicine. Her academic and professional interests are centered on community medicine, preventive healthcare, epidemiology, and public health research. She is involved in teaching, clinical training, and research activities aimed at improving population health and strengthening evidence-based healthcare practices. Email: drpriya.cm@gmail.com