International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Correlation Between Thyroid Autoantibodies and Recurrent Pregnancy Loss: A Cross-Sectional Study

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Received: 01-05-2026
Accepted: 25-06-2026
Available online: 30-06-2026

ABSTRACT

Introduction: Recurrent pregnancy loss (RPL) is a multifactorial disorder of reproduction and thyroid autoimmunity can play a role even if thyroid hormone levels are within normal range. To assess the relationship between thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) with RPL and to investigate the correlation between antibody titres, thyrotropin and pregnancy loss.

Methods: This cross-sectional comparative study comprised 220 euthyroid women aged 20-38 years, 110 women with two or more pregnancy losses prior to 20 weeks gestation and 110 controls with at least one live birth and no miscarriage. Chemiluminescent immunoassay was used to measure serum thyrotropin, free thyroxine, TPOAb, and TgAb. Group comparisons were carried out, Spearman correlation was done, trend testing was done and multivariable logistic regression was carried out.

Results: Any thyroid autoantibody was detected in 43/110 women with RPL (39.1%) and 19/110 controls (17.3%; p<0.001). TPOAb positivity was more frequent in the RPL group (32.7% vs 13.6%; p=0.001), as was TgAb positivity (25.5% vs 10.0%; p=0.003). Median TPOAb and TgAb titres were higher for two, three, and four or more losses (p for trend<0.001 and 0.006, respectively). The number of losses correlated with TPOAb titre (r=0.34, p<0.001), TgAb titre (r=0.25, p<0.001), and thyrotropin (r=0.19, p=0.005). Any antibody positivity was still associated with RPL after adjustment for age, BMI, parity, thyrotropin and family history of thyroid disease (adjusted odds ratio 2.83; 95% CI 1.48-5.41; p=0.002).

Conclusion: Thyroid autoantibodies were significantly more common in women with RPL who were euthyroid and were dose-response related to loss burden. Standard RPL evaluation can be supplemented by antibody testing, but this needs to be studied in prospective trials to establish causality and treatment implications.

Keywords: *recurrent pregnancy loss; thyroid autoimmunity; thyroid peroxidase antibody; thyroglobulin antibody; miscarriage; euthyroid women.*

INTRODUCTION

Recurrent pregnancy loss is generally considered to be the failure of two or more pregnancies and is a clinically and psychologically significant reproductive failure. Modern teaching focuses on the fact that RPL is not monogenous and can be due to genetic, anatomical, endocrine, thrombotic, immunological and lifestyle-related mechanisms, and a significant proportion of cases has no explanation despite conventional evaluation [1].

Maternal age, previous pregnancy losses, and the presence of a treatable cause are factors that affect the chances of a successful subsequent pregnancy. Structured assessment is recommended but not indiscriminate testing that has little prognostic or therapeutic value. Major RPL guidance includes thyroid function testing and assessment for thyroid

peroxidase antibodies as these tests can provide information on thyroid function and may help identify a biologically distinct group, which is treatable for thyroid dysfunction.

The thyroid peroxidase antibody and thyroglobulin antibody are markers of autoimmune thyroid disease. They can be present before biochemical hypothyroidism and can be a sign of decreased thyroidal reserve in the metabolic stress of conception and early gestation. Before and during pregnancy, women should be evaluated with caution using thyrotropin, free thyroxine, antibody status, and pregnancy-specific reference ranges, as recommended by the American Thyroid Association [2-3].

There have been several reports of an association between thyroid autoantibodies and miscarriage in euthyroid populations. A large meta-analysis showed that antibody-positive women were more likely to experience miscarriage and preterm birth than antibody-negative women, indicating that the association is not just due to overt thyroid hormone deficiency [4].

A second meta-analysis also found that women with thyroid autoimmunity had an increased risk of miscarriage when they were euthyroid. Theories have suggested that there may be a subtle impairment of thyroid reserve, a generalized autoimmunity, changes in maternal immune tolerance, direct effects of antibodies, and confounding by age or other reproductive factors [5].

Increased levels of TPOAb and TgAb have been found in women with recurrent miscarriage in case-control studies. Ticconi and colleagues also noted that co-positivity of the two antibody markers might offer greater discrimination than either marker alone, which would support the use of both major thyroid autoantibodies in etiological studies [6].

Not all studies have shown a direct relationship between antibody status and subsequent live birth. Thyroid antibodies were relatively prevalent in a large untreated population of women with recurrent miscarriage, but were not alone a good predictor of the next pregnancy outcome, suggesting that antibody positivity may be a risk marker rather than a deterministic cause [7].

In more recent cross-sectional studies, thyroid autoimmunity has been consistently associated with RPL, although the extent of this association has been affected by the population iodine status, the definition of thyroid autoimmunity, maternal age, the number of previous miscarriages, and exclusion of women with known causes of miscarriage [8].

Studies are still needed that compare antibody prevalence in fertile controls, measure antibody titres instead of just dichotomizing results, and determine whether antibody burden is associated with the number of losses after controlling for appropriate covariates. The present study therefore aimed to assess the association between TPOAb and TgAb and RPL in euthyroid women and to determine the relationship of antibody titres and thyrotropin with cumulative pregnancy-loss burden.

MATERIALS AND METHODS

This was a cross sectional comparative study of the departments of obstetrics and gynecology, reproductive medicine and biochemistry of a tertiary teaching hospital. The women who attended the recurrent pregnancy loss clinic were consecutively selected and were included as cases. Women who received routine gynecological or preconception care during the same time period served as controls.

Participants

The RPL group consisted of women aged 20-38 years who had two or more spontaneous clinically recognized pregnancy losses before 20 completed weeks. The control group consisted of women of the same age frequency with at least one spontaneous live birth, no previous miscarriage and no history of infertility. At the time of sampling, all participants were not pregnant and their serum free thyroxine was within the laboratory reference interval.

Eligibility criteria

Women were excluded if they had overt hypothyroidism or hyperthyroidism, current levothyroxine or antithyroid-drug use, previous thyroid surgery or radioiodine treatment, diabetes mellitus, chronic renal or hepatic disease, systemic autoimmune disease, antiphospholipid syndrome, known parental chromosomal abnormality, major uterine anomaly, active infection, or use of immunomodulatory medication. Women who had a pregnancy loss due to a known fetal chromosomal defect were also not included in the main analysis.

Sample size

The sample size was determined for a two-sided comparison of antibody prevalence in women with RPL and controls. With 90% power and an alpha of 0.05, 101 women with RPL and 101 controls would be needed if the prevalence of thyroid autoantibody positivity was 32% in women with RPL and 14% in controls. Due to the possibility of incomplete laboratory results, 110 women were added to each group, resulting in a total of 220 women.

Clinical assessment
The structured interview included data on age, residence, education, smoking exposure, menstrual characteristics, gravidity, parity, gestational age at each loss, family history of thyroid disease, and previous infertility treatment. Body height and weight were measured without shoes and used calibrated instruments, body mass index was calculated as kg/m2. The available records of pelvic ultrasonography, parental karyotyping, antiphospholipid testing and products-of-conception analysis were examined.

Laboratory measurements
Blood was drawn after an overnight fast between 08:00 and 10:00. Within 60 minutes, serum was separated and analysed on an automated chemiluminescent immunoassay platform. Thyrotropin, free thyroxine, TPOAb and TgAb were determined in duplicate using manufacturer quality-control procedures. Euthyroidism was considered to be defined as having normal free thyroxine and thyrotropin between 0.40 and 4.00 mIU/L. TPOAb values >34 IU/mL and TgAb values >115 IU/mL were deemed positive. Any thyroid autoimmunity was defined as positivity for either antibody.

Outcome measures
The main outcome was the presence of any thyroid autoantibody in the RPL and control groups. Secondary outcomes included individual TPOAb and TgAb positivity, antibody titres, thyrotropin level, correlations between laboratory markers and number of pregnancy losses, and adjusted associations between thyroid markers and RPL.

Statistical analysis
The data were analysed using SPSS version 29.0. The Shapiro-Wilk test was used to determine the normality of continuous variables. Data were normally distributed and are reported as mean +/- standard deviation and compared using the independent-samples t test. Data were skewed and presented as median and interquartile range and compared using the Mann-Whitney U test. The chi-square or Fisher exact test was used to compare categorical variables. Spearman correlation was used to evaluate the relationship between antibody titres, thyrotropin and number of losses. An antibody positivity trend test was conducted in the loss categories using a Cochran-Armitage test. Variables with clinical relevance and $p<0.10$ in univariable analysis were included in the multivariable logistic regression analysis. Odds ratios (with 95% confidence intervals) are presented. A $p<0.05$ was regarded as statistically significant for a two-tailed test.

RESULTS
A total of 254 women were screened. Twenty-one did not meet eligibility criteria, nine declined participation, and four had incomplete antibody results. The final analysis included 220 women, with 110 in each group. The mean age was 29.8 +/- 4.1 years in the RPL group and 29.2 +/- 4.0 years among controls (p=0.28). Body mass index and menstrual-cycle length were also comparable. Women with RPL had greater gravidity and lower parity, consistent with the study definition. Baseline characteristics are shown in Table 1.

Any thyroid autoantibody was present in 39.1% of women with RPL compared with 17.3% of controls ($p<0.001$). TPOAb positivity was 32.7% versus 13.6% (p=0.001), while TgAb positivity was 25.5% versus 10.0% (p=0.003). Median antibody titres were higher in the RPL group for both markers. Although all participants were euthyroid, mean thyrotropin was modestly higher among women with RPL (2.86 +/- 0.91 vs 2.31 +/- 0.82 mIU/L; $p<0.001$), while free thyroxine did not differ significantly (Table 2).

Within the RPL group, 49 women had two losses, 34 had three losses, and 27 had four or more losses. Any antibody positivity increased from 28.6% to 41.2% and 55.6% across these categories (p for trend=0.006). The number of losses correlated with TPOAb titre (r=0.34, $p<0.001$), TgAb titre (r=0.25, $p<0.001$), and thyrotropin (r=0.19, p=0.005). In multivariable analysis, any antibody positivity was independently associated with RPL (adjusted OR 2.83; 95% CI 1.48-5.41; p=0.002). TPOAb positivity, TgAb positivity, and thyrotropin at or above 2.5 mIU/L also retained significant associations (Table 3).

Table 1. Baseline characteristics of women with recurrent pregnancy loss and controls

Characteristic	RPL group (n=110)	Control group (n=110)	p-value
Age, years	29.8 +/- 4.1	29.2 +/- 4.0	0.28
Body mass index, kg/m2	24.9 +/- 3.7	24.3 +/- 3.5	0.21
Cycle length, days	29.1 +/- 3.2	28.7 +/- 3.0	0.34
Gravidity, median (IQR)	3 (2-4)	2 (1-3)	<0.001
Parity, median (IQR)	0 (0-1)	1 (1-2)	<0.001

Characteristic	RPL group (n=110)	Control group (n=110)	p-value
Family history of thyroid disease, n (%)	19 (17.3)	9 (8.2)	0.043
Previous infertility treatment, n (%)	17 (15.5)	6 (5.5)	0.015
Current passive smoke exposure, n (%)	20 (18.2)	17 (15.5)	0.59

RPL, recurrent pregnancy loss; IQR, interquartile range. Values are mean +/- SD unless otherwise stated.

Table 2. Thyroid function and thyroid autoantibodies by study group

Laboratory measure	RPL group (n=110)	Control group (n=110)	p-value
Thyrotropin, mIU/L	2.86 +/- 0.91	2.31 +/- 0.82	<0.001
Free thyroxine, ng/dL	1.16 +/- 0.16	1.18 +/- 0.15	0.32
TPOAb titre, IU/mL, median (IQR)	24 (11-88)	13 (7-27)	<0.001
TgAb titre, IU/mL, median (IQR)	62 (24-181)	31 (17-72)	<0.001
TPOAb positive, n (%)	36 (32.7)	15 (13.6)	0.001
TgAb positive, n (%)	28 (25.5)	11 (10.0)	0.003
Both antibodies positive, n (%)	21 (19.1)	7 (6.4)	0.005
Any antibody positive, n (%)	43 (39.1)	19 (17.3)	<0.001
Thyrotropin >=2.5 mIU/L, n (%)	66 (60.0)	39 (35.5)	<0.001

TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; IQR, interquartile range.

Table 3. Correlations and multivariable associations with recurrent pregnancy loss

Predictor	Effect estimate	95% CI	p-value
TPOAb titre vs number of losses	Spearman r=0.34	0.21 to 0.45	<0.001
TgAb titre vs number of losses	Spearman r=0.25	0.12 to 0.37	<0.001
Thyrotropin vs number of losses	Spearman r=0.19	0.06 to 0.31	0.005
Any antibody positivity	Adjusted OR=2.83	1.48 to 5.41	0.002
TPOAb positivity	Adjusted OR=2.62	1.28 to 5.35	0.008
TgAb positivity	Adjusted OR=2.31	1.05 to 5.08	0.038
Thyrotropin >=2.5 mIU/L	Adjusted OR=1.91	1.07 to 3.42	0.029
Family history of thyroid disease	Adjusted OR=1.77	0.73 to 4.30	0.21

Logistic models were adjusted for age, body mass index, parity, previous infertility treatment, family history of thyroid disease, and thyrotropin. OR, odds ratio; CI, confidence interval.

DISCUSSION

Thyroid autoimmunity was significantly more common in euthyroid women with RPL than in fertile women. After adjusting for age, BMI, parity, infertility treatment, family history of thyroid disease, and thyrotropin, positivity for either TPOAb or TgAb continued to be associated with RPL. There was also a moderate correlation between antibody titres and thyrotropin, and the number of losses.

The difference between cases and controls observed in this study is similar to that reported previously for higher prevalence of TPOAb and TgAb in women with recurrent miscarriage [6]. The absolute prevalence differs among studies due to differences in iodine status, assay platforms, antibody thresholds, maternal age and definition of RPL. However, recent clinical data also have shown that thyroid autoimmunity is a meaningful subset of women who are evaluated for RPL [8]. The cross sectional design does not allow for the detection of a dose-response relationship, but the trend from 2 to 4+ losses to antibody positivity suggests a biological gradient. Thyroid antibody can detect a thyroid reserve deficit and apparently euthyroid women may not be able to compensate for the increased endocrine requirements of early gestation and implantation. They can also be a reflection of more general immune dysfunction that could include trophoblast invasion, cytokine balance, complement activation, or maternal-fetal tolerance.

The evidence for prospective is less consistent. Some cohorts have reported a decreased probability of live birth with antibody positivity [9] while other untreated RPL cohorts have reported that antibody positivity alone was not a reliable predictor of the next pregnancy outcome [7]. The results suggest that thyroid autoimmunity should be considered as a part of the multifactorial risk for miscarriage rather than a cause of it.

Subclinical hypothyroidism and thyroid autoimmunity have been reported to be associated with RPL by a meta-analysis [10]. Association does not imply treatment benefits, however. The TABLET trial did not show a live-birth benefit for women with RPL who were antibody positive and euthyroid and were treated with routine levothyroxine [11] and the T4LIFE trial did not support routine levothyroxine for TPOAb-positive, euthyroid women with RPL [12]. Treatment should therefore be based on the presence of confirmed thyroid dysfunction and on the current recommendations of the guidelines, and not only on antibody positivity.

The strengths of the present study are the contemporaneous recruitment, evaluation of both major thyroid autoantibodies, duplicate laboratory measurement, exclusion of overt thyroid disease, and adjustment for clinically relevant covariates. In addition to the positive versus negative comparison, antibody titres were analysed and categories of losses were determined. The major drawbacks are the cross-sectional design, single centre location and the absence of the ability to determine whether the losses preceded the antibodies. There may be residual confounding due to unmeasured genetic, immunological, nutritional, or environmental factors. Laboratory thresholds are assay-specific and exclusion of known causes of miscarriage may restrict generalizability to unselected RPL clinics. The outcomes of pregnancies following enrolment were not assessed.

From a clinical perspective, thyroid function testing is still relevant in a logical RPL evaluation. Measurement of TPOAb may aid in the identification of women who should be monitored more closely for the development of hypothyroidism, particularly if thyrotropin is high-normal or elevated. The findings do not justify broad immunological treatment, but may provide information in selected antibody-negative patients. Longitudinal, multicentre studies are needed to establish if antibody titre trajectories contribute additional predictive power to maternal age, loss history and thyroid function.

There is further literature that offers a more complex understanding of antibody positivity. Thyroid autoimmunity has been long identified as a marker that is linked to miscarriage risk, and there is a lack of clarity about direct causality [13]. In a preliminary case-control study, higher thyroid antibody levels were observed in non-pregnant women with recurrent spontaneous abortion who were euthyroid [14]. More recent cohorts have linked TPOAb positivity to women who had otherwise unexplained recurrent first-trimester miscarriage in euthyroid women [15].

Antibody-positive women may have reduced live-birth rates in some settings [16] but reviews of pregnancy outcomes warn that age, thyrotopin, iodine status, and other coexisting autoimmunity are significant confounders [17]. Recent randomized trials have been accompanied by commentary that concludes that routine levothyroxine treatment of euthyroid TPOAb-positive RPL is not supported and that surveillance for emerging thyroid dysfunction is appropriate [18].

CONCLUSION

Thyroid autoantibodies were significantly higher in women with recurrent pregnancy loss who were euthyroid compared to fertile controls. Positive correlations between TPOAb and cumulative loss burden were observed and antibody positivity remained independently associated with RPL after adjusting for relevant covariates. Thyroid autoimmunity may thus serve as a helpful risk marker in a comprehensive evaluation, but should not be used to help make treatment decisions until prospective evidence and randomized trials have been completed.

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