Vol. 4 No. 4 (2025)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Progesterone and Luteal Phase Deficiency: Endocrinological Insights into Recurrent Pregnancy Loss

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Keywords: Recurrent Pregnancy Loss; Progesterone; Luteal Phase Deficiency; Endocrine Dysfunction; Prolactin; Thyroid Function.

Received on 15 August 2025
Accepted on 10 November 2025
Published on 20 November 2025

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Abstract

Background: Recurrent pregnancy loss (RPL) is a complicated conceptual conceptional reproduction illness in which endocrine malfunctions particularly the malfunctioning of luteal phase that is increasingly becoming an issue of speculation as factors which can be modified. The role of progesterone in endometrial receptivity, implantation and maintenance of early pregnancy is a major topic, yet its clinical role in RPL has been under-valued.

Objective: To determine the luteal phase features and mid-luteal hormonal levels in women of recurrent pregnancy loss and to determine independent endocrine predictors of pregnancy loss.

Methods: It was an analytical case-control study involving 60 women who had recurrent pregnancy loss and 60 women who had healthy fertility. Luteal phase length was measured and mid-luteal follicle-stimulating hormone, prolactin, progesterone, luteinizing hormone, estradiol, and thyroid-stimulating hormone were measured.

Univariate analysis was done to measure the associations between luteal phase parameters and RPL, and multivariate logistic regression was used to determine independent predictors.
Results: Compared to controls, RPL women had a high short luteal phases and low mid-luteal progesterone levels. The low concentration of progesterone (less than 10 ng/mL) and short luteal phase (less than 10 days) were found to be strongly related to the risk of RPL. The higher levels of prolactin and thyroid malfunction were also very high in the RPL group. Multivariate analysis has revealed that progesterone insufficiency, a short luteal phase, increased body mass index, and thyroid dysfunction were still independent predictors of recurrent pregnancy loss.
Conclusion: Repeated pregnancy loss is closely linked with progesterone deficiency and functional luteal phase inadequacy, which is usually accompanied by other endocrine disorders. A thorough assessment of the luteal phase activity and specific endocrine screening could enhance the process of risk stratification and personal approach to treatment in women with recurrent pregnancy loss.

Introduction

Recurrent pregnancy loss (RPL) is a painful reproductive condition, which is typically outlined as two or more consecutive pregnancy losses throughout the time of the fetus viability. It is a disease that occurs in about 1-2% of reproductive age women and is to date a considerable challenge in clinical care notwithstanding reproductive medicine (1). Although genetic, anatomical, immunological, and infectious causes play a role in RPL, endocrine abnormalities have become a key area of study as modifiable and clinically implementable RPL causes (2). Among endocrine factors, progesterone plays a central role in the establishment and maintenance of early pregnancy. Progesterone is essential for endometrial receptivity, decidualization, immune tolerance, and early placental development (3). Poor implantation and poor early embryonic growth may be caused by insufficient exposure to progesterone at the luteal phase, which may lead to pregnancy loss (4). Therefore, a mechanistic relationship between luteal phase dysfunction and RPL is suggested by progesterone insufficiency.

Luteal phase deficiency (LPD) can be described as insufficient secretion of progesterone, declining luteal phase, or the response of endometrium to progesterone (5). Despite the decades of discussion of the concept of LPD, the growing body of evidence is that functional luteal inadequacy, not isolated biochemical thresholds, may be of clinical importance in women with unexplained pregnancy loss (6). Reduced luteal lengthening and suboptimal mid luteal levels of progesterone have been repeatedly seen to be present in women with recurring miscarriage (7). The biological effects of progesterone are not limited to the endometrial maturation. It adjusts the activity of natural killer cells in the uterus and enhances the Th2-dominant immune response and suppresses the inflammatory cytokines that otherwise interfere with early pregnancy (8). Deficiency in signaling by progesterone may therefore be a risk factor for implantation failure or early placental insufficiency in which case ovulation appears normal clinically (9).

Endocrinological upsets are often found in association with luteal dysfunction. Hyperprolactinemia has been shown to disrupt the gonadotropin-releasing hormone pulsatility and corpus luteum function, resulting in decreased progesterone secretion (10). Similarly thyroid dysfunction especially subclinical hypothyroidism has been associated with impaired luteal progesterone production and poor pregnancy outcomes (11). These interactions make it important to have an extensive hormonal evaluation in RPL women. Despite increased understanding of the importance of progesterone, the diagnostic criteria for LPD are still inconsistent and clinical practice is therefore highly variable. Many guidelines do not recommend sporadic evaluation of the luteal phase,

in part because of heterogeneity in the diagnostic methods and lack of information on clinical thresholds (12). As a consequence, potentially correctable endocrine abnormality can be missed in women with recurrent pregnancy loss. Recent studies have put more emphasis on the importance of integrated assessment like luteal phase length, serum progesterone levels and associated hormonal disturbances, and not just one parameter (13). Understanding the relative contribution of progesterone insufficiency in the larger scheme of endocrine milieu may help better tailor what diagnostic strategies are optimal as well as propose targeted therapeutic interventions.
Given these considerations, the aims of the present study are to offer endocrinological insights to the role of progesterone and luteal phase deficiency-related to recurrent pregnancy loss-between women with RPL and healthy controls, and identify independent predictors of pregnancy loss (multivariable analysis).

Materials and Methods

Study Design and Setting

This study was performed in the form of an analytical case control study aimed to assess the luteal phase characteristics and endocrine parameters in women with recurrent pregnancy loss and healthy controls. The study was conducted in the Department of Gynecology and Obstetrics with the endocrinology laboratory of the affiliated tertiary care hospital. Recruitment and data collection was carried out during a specific study period.

Study Population

A total of 120 women of reproductive age were enrolled and divided into two groups:
(i) women with a history of recurrent pregnancy loss (RPL group, n = 60), and
(ii) healthy fertile women with at least one successful pregnancy and no history of miscarriage (control group, n = 60). Recurrent pregnancy loss was defined as two or more consecutive spontaneous pregnancy losses occurring before 20 weeks of gestation, consistent with contemporary clinical guidelines (14).

Inclusion Criteria

Participants were included in the study if they met all of the following criteria:
Women aged 20–40 years
Regular menstrual cycles (25–35 days)
Confirmed ovulatory cycles
History of ≥2 consecutive pregnancy losses for the RPL group
At least one live birth with no prior miscarriage for the control group
These criteria were selected to ensure hormonal comparability and reduce confounding due to age-related or cycle-related variability (15).

Exclusion Criteria

Participants were excluded if any of the following were present:
Congenital or acquired uterine anomalies
Chromosomal abnormalities in either partner
Diagnosed autoimmune disorders (e.g., antiphospholipid syndrome)
Diabetes mellitus or uncontrolled systemic illness
Polycystic ovary syndrome (PCOS)
Use of hormonal medications within the preceding three months
Exclusion criteria were applied to eliminate established causes of miscarriage unrelated to luteal endocrine dysfunction (16).

Assessment of Luteal Phase Characteristics

Luteal phase length was calculated as the number of days between ovulation and the onset of menstruation. Ovulation was determined using mid-cycle ultrasonography and/or serum luteinizing hormone (LH) surge detection. A luteal phase duration of ≤10 days was considered shortened and suggestive of luteal phase deficiency, based on previously published endocrinological thresholds (17).

Hormonal Evaluation

Blood samples were collected during the mid-luteal phase (7 days post-ovulation). Serum levels of progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, prolactin, and thyroid-stimulating hormone (TSH) were measured using standardized chemiluminescent immunoassays. A serum progesterone concentration of <10 ng/mL in the mid-luteal phase was considered indicative of inadequate luteal progesterone support (18).

Statistical Analysis

Data were analyzed on standard statistical software. Continuous variables were tested for normality and reported as mean declared plus standard deviation or medians declared plus interquartile ranges, as was suitable. Group comparisons were conducted with the independent t-test or the Mann-Whitney U test for continuous variables, and using the chi-square test for categorical variables. Univariate odds ratios (ORs) and 95% confidence intervals (CIs) were computed to assess the relationship between parameters within the luteal phase and recurrent pregnancy loss. Variables with biological relevance or statistical significance were entered in a multivariable logistic regression model to identify independent prognostic factors of RPL. P-value less than 0.05 was considered statistically significant (19).

Results and Discussion

Baseline Characteristics of Study Participants

A total of 120 women were included in the study, comprising 60 women with recurrent pregnancy loss (RPL group) and 60 fertile women without a history of miscarriage (control group). Baseline demographic and reproductive characteristics are presented in **Table 1** and summarized in **Figure 1**.

Table 1: Baseline Characteristics of Study Participants

Variable	RPL Group (n=60)	Control Group (n=60)	p-value
Age (years)	29.8 ± 4.6	28.9 ± 4.2	0.28
BMI (kg/m²)	26.1 ± 3.4	24.9 ± 3.1	0.04
Gravidity	3 (2–4)	2 (1–3)	<0.001
Parity	0 (0–1)	1 (0–2)	<0.001
Previous miscarriages	2.4 ± 0.7	—	—
Luteal phase length (days)	9.6 ± 1.4	12.3 ± 1.6	<0.001
Luteal phase ≤10 days	38 (63.3%)	9 (15.0%)	<0.001

The mean age of participants did not differ significantly between the two groups (29.8 ± 4.6 years in the RPL group vs. 28.9 ± 4.2 years in controls; p = 0.28). Body mass index (BMI) was significantly higher in the RPL group compared to controls (26.1 ± 3.4 vs. 24.9 ± 3.1 kg/m²; p = 0.04). Reproductive history differed markedly between groups. Women with RPL had higher gravidity and significantly lower parity than controls (p < 0.001 for both). The mean number of previous miscarriages in the RPL group was 2.4 ± 0.7. Luteal phase characteristics also showed significant variation. The mean luteal phase length was shorter in the RPL group compared with controls (9.6 ± 1.4 vs. 12.3 ± 1.6 days; p < 0.001). A luteal phase duration of ≤10 days was observed

in 63.3% of women in the RPL group compared with 15.0% in the control group ($p < 0.001$).

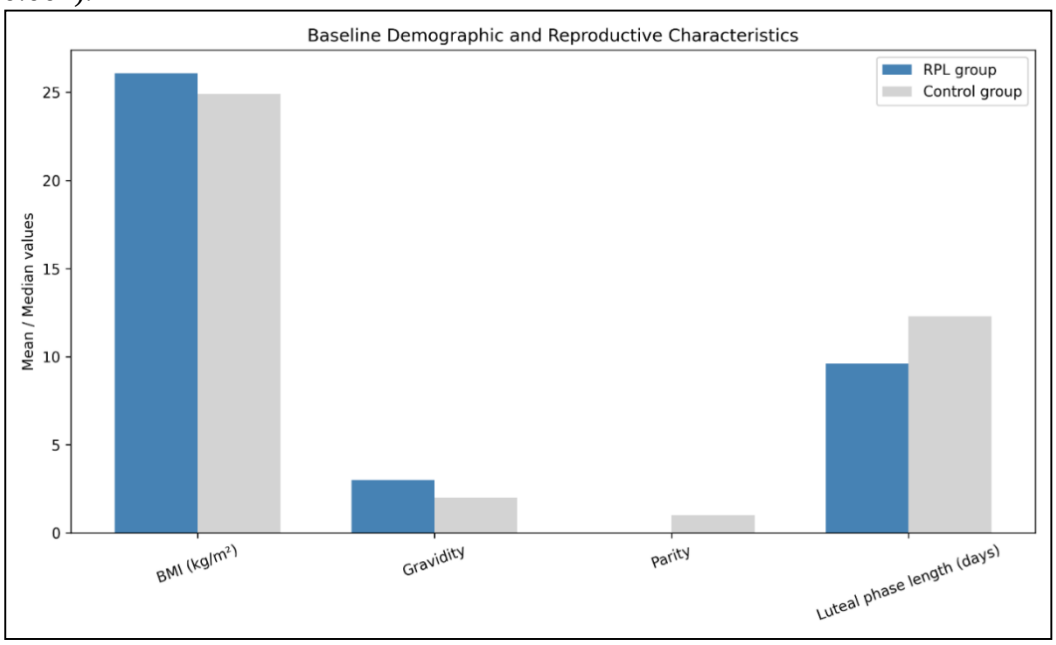

Figure 1: Comparison of baseline demographic and reproductive characteristics between women with recurrent pregnancy loss and controls.

Mid-Luteal Hormonal Profile

Mid-luteal phase hormonal parameters are shown in **Table 2** and illustrated in **Figure 2**. Serum progesterone levels were significantly lower in women with RPL than in controls (7.8 ± 2.9 vs. 13.6 ± 4.1 ng/mL; $p < 0.001$). A progesterone concentration below 10 ng/mL was present in 68.3% of women with RPL compared with 23.3% of controls ($p < 0.001$).

Table 2: Mid-Luteal Hormonal Profile

Parameter	RPL Group	Control Group	p-value
Progesterone (ng/mL)	7.8 ± 2.9	13.6 ± 4.1	<0.001
Progesterone <10 ng/mL	41 (68.3%)	14 (23.3%)	<0.001
LH (IU/L)	6.2 ± 1.8	6.8 ± 1.7	0.08
FSH (IU/L)	7.1 ± 1.9	6.6 ± 1.6	0.12
Estradiol (pg/mL)	162 ± 38	176 ± 42	0.07
Prolactin (ng/mL)	22.4 ± 6.1	17.9 ± 5.2	<0.001
TSH (mIU/L)	3.1 ± 1.2	2.4 ± 0.9	0.002

No statistically significant differences were observed between groups for luteinizing hormone (LH), follicle-stimulating hormone (FSH), or estradiol levels. However, prolactin levels were significantly higher in the RPL group than in the control group (22.4 ± 6.1 vs. 17.9 ± 5.2 ng/mL; $p < 0.001$). Thyroid-stimulating hormone (TSH) levels were also significantly elevated in women with RPL compared to controls (3.1 ± 1.2 vs. 2.4 ± 0.9 mIU/L; $p = 0.002$).

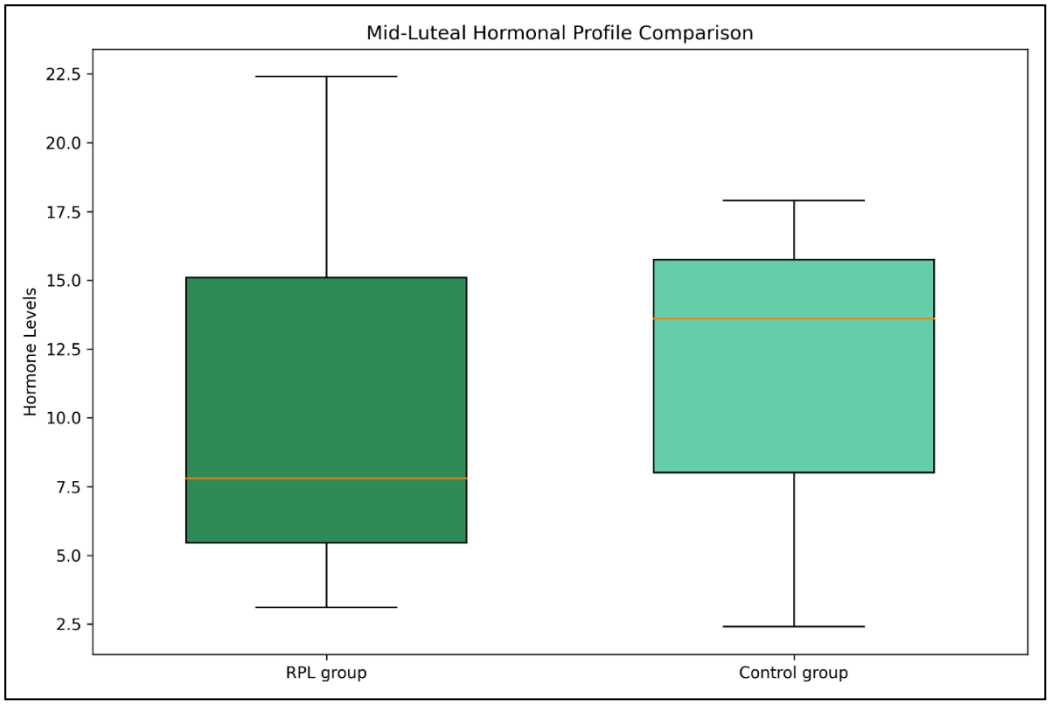

Figure 2: Comparison of mid-luteal hormonal profiles between women with recurrent pregnancy loss and controls.

Association Between Luteal Phase Parameters and Recurrent Pregnancy Loss
Univariate analysis examining the association between luteal phase abnormalities and recurrent pregnancy loss is presented in **Table 3** and depicted in **Figure 3**.

Table 3: Association Between Luteal Phase Parameters and RPL

Risk Factor	RPL	Controls	OR (95% CI)	p-value
Luteal phase ≤10 days	38	9	9.8 (4.1–23.3)	<0.001
Progesterone <10 ng/mL	41	14	7.1 (3.2–15.6)	<0.001
Elevated prolactin	17	6	3.6 (1.3–9.7)	0.01
Thyroid dysfunction	11	4	3.1 (1.0–9.6)	0.04

A luteal phase duration of ≤10 days was strongly associated with RPL (OR = 9.8; 95% CI: 4.1–23.3; $p < 0.001$). Similarly, mid-luteal progesterone levels below 10 ng/mL were significantly associated with increased odds of RPL (OR = 7.1; 95% CI: 3.2–15.6; $p < 0.001$). Elevated prolactin levels were associated with a higher risk of recurrent pregnancy loss (OR = 3.6; 95% CI: 1.3–9.7; $p = 0.01$). Thyroid dysfunction was also significantly associated with RPL (OR = 3.1; 95% CI: 1.0–9.6; $p = 0.04$).

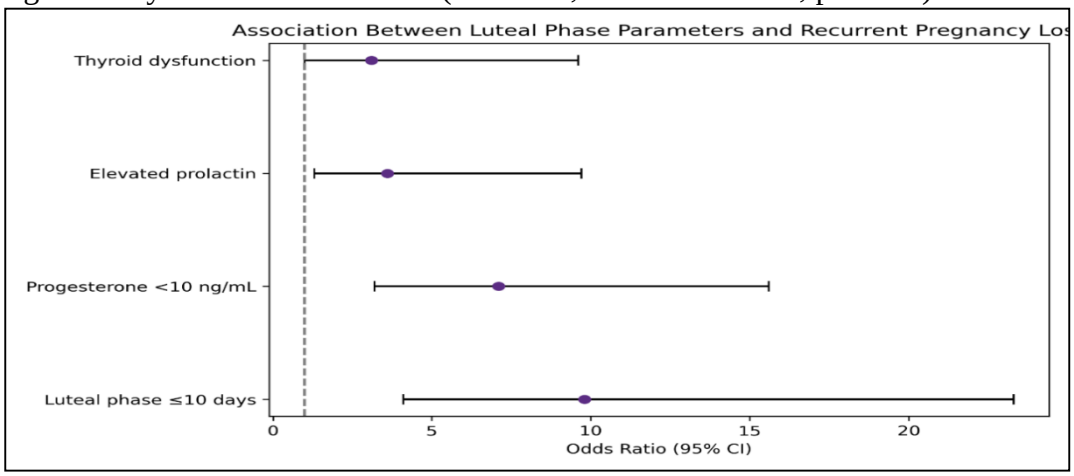

Figure 3: Association between luteal phase abnormalities and recurrent pregnancy loss.

Multivariable Logistic Regression Analysis

Results of the multivariable logistic regression analysis are shown in **Table 4** and summarized in **Figure 4**. After adjustment for potential confounders, serum progesterone concentration remained an independent predictor of RPL, with each 1 ng/mL increase associated with reduced odds of pregnancy loss (adjusted OR = 0.83; 95% CI: 0.75–0.92; $p < 0.001$).

Table 4: Multivariable Logistic Regression Analysis

Variable	β (SE)	Adjusted OR	95% CI	p-value
Progesterone (per 1 ng/mL)	−0.18 (0.05)	0.83	0.75–0.92	<0.001
Luteal phase ≤10 days	1.94 (0.52)	6.96	2.5–19.4	<0.001
BMI (kg/m²)	0.09 (0.04)	1.09	1.01–1.18	0.03
Thyroid dysfunction	1.12 (0.49)	3.07	1.2–8.0	0.02

A luteal phase duration of ≤10 days was independently associated with recurrent pregnancy loss (adjusted OR = 6.96; 95% CI: 2.5–19.4; $p < 0.001$). BMI was also an independent predictor, with increasing BMI associated with higher odds of RPL (adjusted OR = 1.09; 95% CI: 1.01–1.18; $p = 0.03$). Thyroid dysfunction remained significantly associated with RPL after adjustment (adjusted OR = 3.07; 95% CI: 1.2–8.0; $p = 0.02$).

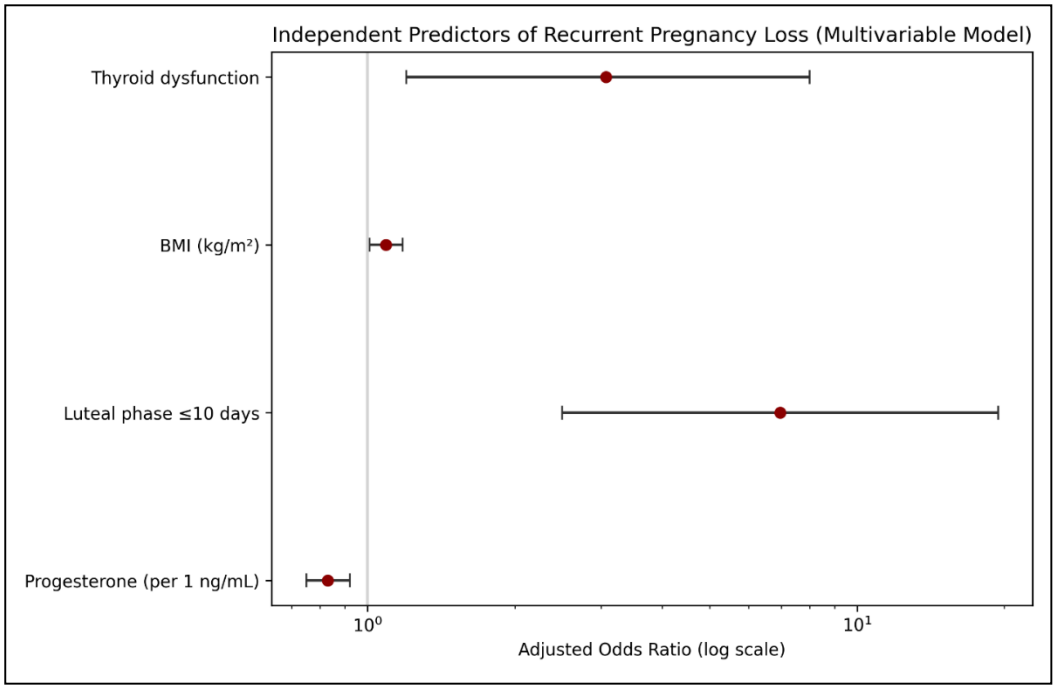

Figure 4: Adjusted odds ratios for independent predictors of recurrent pregnancy loss identified by multivariable logistic regression.

Discussion

The present study demonstrates that recurrent pregnancy loss is closely associated with functional luteal phase disturbances, particularly reduced progesterone support and shortened luteal duration. Although ovulatory markers and gonadotropin profiles were largely preserved, women with RPL showed a pattern consistent with impaired luteal adequacy, supporting the broader view that reproductive failure can occur despite

comparable baseline demographics when endocrine support for early gestation is suboptimal (20). Progesterone is indispensable for early pregnancy maintenance, and inadequate luteal progesterone exposure has long been linked with defective implantation and early pregnancy instability. The progesterone insufficiency is a key central endocrine process that has been observed to contribute to repeated miscarriage, as supported by the results of the observed relationship between progesterone insufficiency noted in low mid-luteal progesterone levels and RPL in this study (21). Significantly, clinical views on progesterone activity in the endometrium also contribute to the opinion that luteal progesterone does not only mark, but it is a functional precondition of receptivity, and early gestational support (22). The normal gynecologic endocrinology models also identify luteal progesterone as an essential variable in successful implantation and pregnancy maintenance (23).

Along with complete deficiency of progesterone, shortening of luteal period proved to be a significant functional predictor of luteal inadequacy. A short luteal phase shortens the duration over which the endometrium is exposed to progesterone, so it is not allowed fully to complete years of secretory maturation and could therefore be more vulnerable during the implantation window. This idea is in line with the evidence that presents the concept of luteal insufficiency and its clinical implication in reproductive failure, especially in women who experience repeated miscarriage (21). It was also found that endocrine comorbidities contribute towards luteal milieu in relation to recurrent pregnancy loss. One of the factors correlated with RPL in a univariate analysis was high levels of prolactin, which is known to affect luteal functionality by changing steroidogenesis of the corpus luteum and endocrine sustenance of implantation. Previous clinical findings explained the relationship between hyperprolactinemia and luteal insufficiency and this leads to prolactin being a viable modifiable variable in this situation (24). More general clinical syntheses also highlight the role of prolactin in reproduction in human beings and how it can disrupt luteal sufficiency and even more so when levels are persistent and or clinically meaningful (25).

The role of the thyroid activity was also clinically significant in the current study, and thyroid dysfunction was linked to RPL on its own. Endometrial functions, placentation and initial gestational stability are affected by thyroid hormones and abnormalities that are caused by thyroid have been widely praised as a factor in infertility and pregnancy loss. The literature on endocrine diagnosis of thyroid disorders in infertile women indicates that a regular thyroid examination is one of the evaluation methods of reproductive endocrinology (26). Further, the mechanistic association between progesterone deficiency and pregnancy loss associated with a lack of endometrial stability and premature gestational support provides support to the biological plausibility of endocrine-mediated reproductive failure (27). The supporting evidence on the benefits of thyroid screening and optimization before and during early pregnancy is supported by evidence that thyroid autoimmunity and hypothyroidism are associated with adverse pregnancy outcome(s) (28).

Lastly, the BMI became a lasting predictor, indicating that the metabolic status can be interacted with the luteal functioning. Obesity has been linked to abnormalities of reproductive endocrine function and pregnancy outcomes, which may be mediated by perturbations in the metabolism of hormones and proinflammatory cytokines resulting in alterations in luteal adequacy and endometrial receptivity (29). The pattern in reproductive-history of women with RPL with significantly lower parity also conforms to known depiction of RPL epidemiology and supports the clinical definition of this group (30). When combined with the current results, a multifactorial endocrine model where functional luteal insufficiency 6reflecting as shortened luteal phase and an inadequate exposure to progesterone is central, and is frequently accompanied by modifiable endocrine factors including prolactin and thyroid disruptions and dependent

on metabolic status. A clinical approach incorporating luteal phase assessment along with targeted endocrine screening may improve risk stratification and support individualized management strategies in women with recurrent pregnancy loss (21).

Conclusion

The research is an excellent example of endocrinological proof of a factor in frequent pregnancy loss being insufficiency of progesterone and luteal phase malfunction. The findings indicated that women who had RPL had much shorter luteal phases and reduced the amount of mid-luteal progesterone in their bodies than the controls and the need to provide sufficient luteal support to establish successful implantation and maintenance of early pregnancy. In addition to the progesterone deficiency, it can be noticed that the contributory roles of high prolactin, thyroid malfunction, and high body mass index also play significant roles even after the factor has been adjusted to multivariates. Consistency of these causes as factors of independent prediction is a reminder that recurrent cases of pregnancy losses is often a by-product of simultaneous endocrine imbalances and not a solitary defect of hormones. Notably, the significant correlation between the short luteal phase and pregnancy loss indicates that functional luteal evaluation could have the diagnostic value other than that of individual hormones. The findings are in favor of a more comprehensive clinical model that involves assessment of the luteal phase features with specific screening of the modifiable comorbid endocrinopathies. Lastly, careful analysis of progesterone levels, luteal phase adequacy and the other endocrine variables can aid in identifying women with recurrent pregnancy loss and come up with unique treatment regimens that can best lead to positive early pregnancy outcomes.

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