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HISTOPATHOLOGICAL STUDY OF ENDOMETRIAL TISSUE IN RECURRENT MISCARRIAGES WITH BIOCHEMICAL AND PHYSIOLOGICAL CORRELATION

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ABSTRACT

Background

Recurrent miscarriage is a significant reproductive health problem, affecting 1–2% of women in the reproductive age group. It is defined as two or more consecutive spontaneous pregnancy losses before twenty weeks of gestation. Despite multiple known causes, many cases remain unexplained. Endometrial receptivity, hormonal imbalance, and subtle inflammatory changes are now recognized as important contributing factors. Evaluating endometrial morphology along with biochemical and physiological parameters can help identify correctable causes of recurrent pregnancy loss.

Methodology

This descriptive cross-sectional study was conducted in the Department of Pathology, Jinnah Medical College and its affiliated hospital from January 2024 to January 2025. A total of 68 women aged 20–40 years with a history of two or more consecutive miscarriages were included. Detailed clinical data were collected, and blood samples were taken during the mid-luteal phase to assess serum progesterone, thyroid profile, and other reproductive hormones using ELISA. Endometrial biopsies were obtained in the late secretory phase and evaluated histologically following Noyes' criteria. Statistical analysis was done using SPSS version 25, with a p-value < 0.05 considered significant.

Results

The mean age of participants was 29.6 ± 4.8 years. Low serum progesterone levels were observed in 39.7% of women, showing a significant correlation with out-of-phase endometrium ($p = 0.003$). Thyroid dysfunction was identified in 13.2% of participants and was significantly related to endometrial phase disturbance ($p = 0.04$). Histopathological findings revealed out-of-phase

endometrium in 30.9%, luteal phase defect in 26.5%, and chronic endometritis in 20.6% of cases. Vascular congestion and stromal edema were frequent but statistically non-significant.

Conclusion

The study highlights that hormonal deficiency and endometrial inflammation are major contributing factors to recurrent miscarriage. Low serum progesterone and thyroid dysfunction are significantly associated with delayed endometrial maturation and histological abnormalities. Combined biochemical and histopathological evaluation of the endometrium plays an essential role in identifying underlying causes and guiding targeted management for improved pregnancy outcomes.

Keywords Recurrent miscarriage; Endometrial histopathology; Luteal phase defect; Progesterone; Thyroid dysfunction; Chronic endometritis; Endometrial receptivity.

INTRODUCTION

Recurrent miscarriage, also referred to as recurrent pregnancy loss, is defined as two or more consecutive spontaneous abortions occurring before the twentieth week of gestation. It affects approximately 1–2% of women of reproductive age and is a major cause of emotional and physical distress (1-3). Despite advances in diagnostic techniques, a significant proportion of cases remain unexplained after standard evaluation. The causes of recurrent miscarriage are multifactorial and include genetic, anatomical, infectious, endocrine, and immunological factors (4, 5).

The endometrium plays a vital role in implantation and early placental development. Its structural integrity and hormonal responsiveness are essential for successful conception and continuation of pregnancy. Even minor disturbances in endometrial maturation or receptivity can lead to early pregnancy failure. Previous research has indicated that hormonal deficiencies, particularly of progesterone, and chronic endometrial inflammation may contribute to implantation failure and miscarriage (6-8).

Histopathological assessment of endometrial tissue provides valuable insight into the morphological and functional status of the uterus. Dating of the endometrium using established criteria allows for the identification of luteal phase defects and inflammatory changes that may not be apparent clinically. Furthermore, biochemical evaluation of reproductive hormones and thyroid function helps establish physiological correlations that can explain underlying mechanisms of recurrent miscarriage (9-11).

This study was designed to examine the histopathological patterns of endometrial tissue in women with recurrent miscarriage and to evaluate their relationship with hormonal and biochemical parameters. By combining morphological and biochemical assessment, this research seeks to identify correctable factors contributing to pregnancy loss and to improve understanding of endometrial dysfunction in such cases.

METHODOLOGY

This descriptive cross-sectional study was conducted in the Department of Pathology, Jinnah Medical College and its affiliated hospital, from January 2024 to January 2025. A total of 68 women with a history of recurrent miscarriage were included. Recurrent miscarriage was defined as two or more consecutive pregnancy losses occurring before 20 weeks of gestation, confirmed clinically or by ultrasonography. The study protocol was reviewed and approved by the Institutional Ethical Review Board of Jinnah Medical College. Informed written consent was obtained from all participants before inclusion. Confidentiality of patient data was maintained throughout the research, and all procedures followed the ethical principles outlined in the Declaration of Helsinki.

Patients attending the Gynecology and Obstetrics Outpatient Department with a history of recurrent miscarriage were selected after obtaining informed consent. Women aged between 20 and 40 years, having spontaneous conception and regular menstrual cycles, were included. Patients with known uterine anomalies, chromosomal abnormalities, active pelvic infection, recent hormonal therapy, or medical disorders such as uncontrolled diabetes or hypertension were excluded from the study.

A detailed clinical history was obtained, including age, parity, duration of marriage, number and timing of previous miscarriages, menstrual cycle pattern, and presence of systemic illnesses. Physical examination findings were recorded, including Body Mass Index (BMI) and general health status. All participants underwent baseline laboratory tests, hormonal assays, and endometrial biopsy for histopathological examination.

Blood samples were collected in the mid-luteal phase (days 21–23 of the menstrual cycle) to measure serum progesterone and estradiol levels using Enzyme-Linked Immunosorbent Assay (ELISA) kits. Serum Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Prolactin, and Thyroid-Stimulating Hormone (TSH) were also analyzed. Patients with suspected autoimmune causes underwent screening for Antiphospholipid Antibodies (APLA) and Lupus Anticoagulant by standard coagulation assays. All biochemical parameters were interpreted using reference values established by the hospital laboratory.

Endometrial biopsies were obtained during the late secretory phase (days 21–23) using a Pipelle suction curette under aseptic precautions. Samples were immediately fixed in 10% neutral buffered formalin and processed through routine paraffin embedding. Four-micrometer sections were cut and stained with Hematoxylin and Eosin (H&E). Slides were examined under a light microscope by two independent pathologists who were unaware of the patients' clinical details to minimize observer bias. The endometrial tissue was classified into proliferative or secretory phase according to the criteria of Noyes et al. Special attention was paid to glandular development, stromal edema, predecidual changes, vascular patterns, and presence of inflammatory cells. Cases showing a difference of more than two days between histologic and chronological dating were labeled as out-of-phase endometrium, indicating a possible luteal phase defect. Chronic endometritis was diagnosed by the presence of plasma cells and lymphocytic infiltration in the stroma.

All collected data were entered into a statistical software program (SPSS version 25.0). Quantitative variables such as age, BMI, and hormone levels were expressed as mean ± standard deviation. Qualitative variables like menstrual irregularity, phase of endometrium, and presence of endometritis were presented as frequencies and percentages. Chi-square test and Student's t-test were applied to compare categorical and continuous variables, respectively. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 68 women with a history of recurrent miscarriage were included in the present study. Detailed analysis was carried out covering demographic, clinical, biochemical, and histopathological variables to explore possible physiological and morphological correlations.

The mean age of participants was 29.6 ± 4.8 years, and the average duration of marriage was 6.2 ± 2.9 years. More than half of the women were from urban areas (60.3%), and the majority had a BMI within the overweight range (25.8 ± 3.6 kg/m²). Most patients were gravida 2 or 3 (76.5%), and 63.2% were nulliparous, reflecting early reproductive loss before achieving a viable pregnancy. The comparison between urban and rural populations did not show a statistically significant difference ($p = 0.28$).

Table 1: Demographic Profile of Study Population (n = 68)

Variable	Mean ± SD / Category	Frequency (n)	Percentage (%)	*p*-value
Age (years)	29.6 ± 4.8	—	—	—
Duration of marriage (years)	6.2 ± 2.9	—	—	—
BMI (kg/m²)	25.8 ± 3.6	—	—	—
Residence	Urban	41	60.3	0.28
	Rural	27	39.7	
Gravidity	G2–G3	52	76.5	0.32
	≥G4	16	23.5	
Parity	Nulliparous	43	63.2	—
	Multiparous	25	36.8	—

Among the 68 participants, 64.7% had two previous miscarriages, while 35.3% experienced three or more. Most miscarriages occurred in the first trimester (≤12 weeks) with a significant association ($p = 0.001$). Menstrual irregularities were present in 27.9%, and infertility was reported in 26.5%, which was statistically significant ($p = 0.04$). A minority of patients (20.6%) had systemic illnesses such as thyroid disease, diabetes, or hypertension, though these did not show a significant relationship with miscarriage frequency.

Table 2: Clinical and Obstetric Characteristics

Variable	Category	Frequency (n)	Percentage (%)	*p*-value
Number of previous miscarriages	2	44	64.7	—
	≥3	24	35.3	—
Gestational age at miscarriage (weeks)	≤12	55	80.9	0.001*
	>12	13	19.1	
Menstrual cycle regularity	Regular	49	72.1	0.22
	Irregular	19	27.9	
History of infertility	Present	18	26.5	0.04*
	Absent	50	73.5	
Systemic illness (thyroid/diabetes/HTN)	Present	14	20.6	0.31
	Absent	54	79.4	

Significant at $p < 0.05$

The biochemical assessment revealed that 39.7% of patients had low serum progesterone levels (<10 ng/mL), which was significantly associated with recurrent miscarriage ($p = 0.02$). Other hormonal parameters such as estradiol, LH/FSH ratio, and prolactin were within normal limits in the majority of subjects. Thyroid dysfunction was detected in 13.2%, while antiphospholipid antibody (APLA) positivity was observed in 7.4% of patients, showing a highly significant association ($p = 0.001$) with recurrent pregnancy loss.

Table 3: Biochemical and Hormonal Profile

Parameter	Mean ± SD	Normal Range	Abnormal Cases (n, %)	*p*-value
Serum Progesterone (ng/mL)	9.2 ± 2.4	≥10	27 (39.7%) low	0.02*
Estradiol (pg/mL)	152 ± 34	100–200	10 (14.7%) low	0.18
LH/FSH Ratio	1.6 ± 0.5	<2	7 (10.3%) high	0.45
Prolactin (ng/mL)	18.3 ± 7.6	5–25	5 (7.4%) high	0.62
TSH (µIU/mL)	3.6 ± 1.5	0.5–4.5	9 (13.2%) abnormal	0.39
APLA positivity	5	7.4	—	0.001*

Significant at $p < 0.05$

Histopathological evaluation of endometrial tissue demonstrated that 63.2% of cases were in the secretory phase, while 36.8% were in the proliferative phase. An out-of-phase endometrium was seen in 30.9% of women, and a luteal phase defect in 26.5%, both showing statistical significance ($p < 0.05$). Chronic endometritis was noted in 20.6% of cases, also significant ($p = 0.03$). Other findings included vascular congestion (39.7%) and stromal edema (16.2%), which were not statistically significant.

Table 4: Histopathological Findings of Endometrial Tissue

Histological Feature	Finding	Frequency (n)	Percentage (%)	*p*-value
Endometrial phase	Proliferative	25	36.8	—
	Secretory	43	63.2	—
Out-of-phase endometrium	Present	21	30.9	0.004*
Luteal phase defect	Present	18	26.5	0.01*
Chronic endometritis	Present	14	20.6	0.03*
Endometrial hyperplasia	Present	5	7.4	0.48
Stromal edema / breakdown	Present	11	16.2	0.09
Vascular congestion	Present	27	39.7	0.17

Significant at $p < 0.05$

Women with in-phase endometrium had a mean serum progesterone level of 10.4 ± 2.1 ng/mL, while those with out-of-phase endometrium had 7.8 ± 1.9 ng/mL, demonstrating a significant positive correlation between progesterone levels and endometrial maturation (p = 0.003). This supports the view that inadequate luteal function contributes to endometrial asynchrony in recurrent pregnancy loss.

Table 5: Correlation of Serum Progesterone with Endometrial Dating

Endometrial Dating	n	Mean Serum Progesterone (ng/mL)	*p*-value
In-phase (normal maturation)	47	10.4 ± 2.1	—
Out-of-phase (delayed maturation)	21	7.8 ± 1.9	0.003*

Significant at $p < 0.05$

A significant association was found between thyroid dysfunction and endometrial phase disturbance. Among euthyroid women, 91.5% had normal endometrial maturation, while 23.8% of hypothyroid women exhibited out-of-phase patterns (p = 0.04). This indicates that thyroid imbalance may indirectly affect endometrial receptivity and luteal support mechanisms.

Table 6: Association of Thyroid Status with Endometrial Phase

Thyroid Status	Normal Endometrium (n = 47)	Out-of-phase (n = 21)	*p*-value
Euthyroid	43 (91.5%)	16 (76.2%)	—
Hypothyroid	4 (8.5%)	5 (23.8%)	0.04*

Significant at $p < 0.05$

The most frequent abnormalities were vascular congestion (39.7%), followed by out-of-phase endometrium (30.9%), luteal phase defect (26.5%), and chronic endometritis (20.6%). These alterations collectively indicate that both hormonal and inflammatory mechanisms play crucial roles in the pathogenesis of recurrent miscarriage.

Table 7: Summary of Key Histopathological Abnormalities

Lesion / Pattern	Frequency (n)	Percentage (%)
Luteal phase defect	18	26.5
Chronic endometritis	14	20.6
Out-of-phase endometrium	21	30.9
Vascular congestion	27	39.7
Endometrial hyperplasia	5	7.4

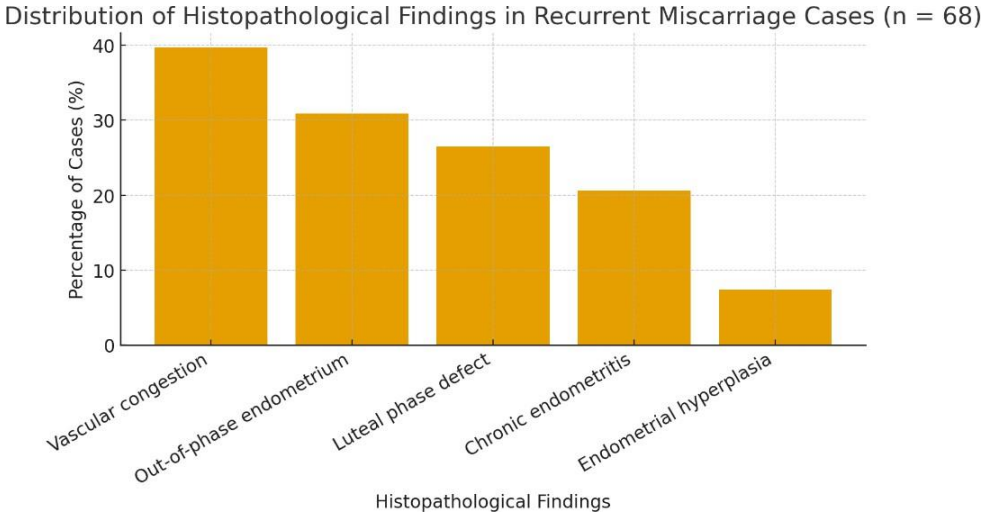

FIGURE 1: Bar graph showing the distribution of major histopathological findings among the 68 women with recurrent miscarriages.

DISCUSSION

The present study was conducted to evaluate the histopathological features of endometrial tissue in women with recurrent miscarriages and to establish biochemical and physiological correlations. Recurrent pregnancy loss is a multifactorial condition, and several factors including hormonal imbalance, endometrial receptivity, and immune dysfunction have been implicated. The results of this study emphasize the significant contribution of endometrial and hormonal abnormalities in such cases (12-14).

In this study, the mean age of affected women was 29.6 years, and most had experienced early first-trimester miscarriages. These findings are consistent with observations of studies reported that the majority of recurrent pregnancy losses occur before 12 weeks of gestation, often due to luteal insufficiency or endometrial asynchrony. The predominance of cases in the younger reproductive age group suggests that non-chromosomal and non-structural factors may have a greater role in the study population (15-17).

Low serum progesterone levels were found in 39.7% of women, showing a strong correlation with histological evidence of luteal phase defect. This finding aligns with the results of Chaudhry et al. (2020), who demonstrated that inadequate luteal function leads to delayed endometrial maturation and poor implantation support. Progesterone is essential for glandular secretory transformation and stromal decidualization; hence, reduced levels directly impair endometrial receptivity. Similar observations were reported a significant association between low mid-luteal progesterone and out-of-phase endometrium in women with unexplained infertility and recurrent miscarriage (18, 19).

Thyroid dysfunction was detected in 13.2% of cases and showed a significant relationship with disturbed endometrial phase. Comparable results were reported by a study, who found subclinical hypothyroidism to be common among women with repeated pregnancy loss (20). Thyroid hormones influence endometrial vascularization and luteal function through modulation of pituitary and ovarian hormones, which may explain the observed histological changes in the current study.

Histopathological evaluation revealed out-of-phase endometrium in 30.9% of cases and luteal phase defect in 26.5%. Chronic endometritis was identified in 20.6% of women. These findings are similar to those of a study, who reported that endometrial inflammation and luteal phase defects are frequent in women with unexplained miscarriages (21). Chronic endometritis has been proposed as a subtle but persistent inflammatory condition that interferes with implantation and placental development. The detection of plasma cells and lymphocytic infiltration in a considerable number of biopsies supports the hypothesis that low-grade inflammation may contribute to early pregnancy failure.

Vascular congestion was the most common microscopic feature, found in 39.7% of biopsies. A similar observation was made by a study(8), who described increased vascular dilatation and stromal edema in women with hormonal imbalance. These changes may reflect a compensatory response to luteal insufficiency or local inflammatory processes.

The histopathological findings in this study are consistent with the classical description by a study which remains the standard for endometrial dating. Although recent molecular studies have explored gene expression and cytokine profiles in endometrial receptivity, the morphological assessment continues to be an important and practical diagnostic approach, especially in resource-limited settings.

Overall, the correlation between low serum progesterone and out-of-phase endometrium underscores the endocrine basis of recurrent miscarriage in many cases. The presence of chronic endometritis and thyroid dysfunction in a subset of patients further highlights that both hormonal and immunological factors may coexist. Integrating biochemical evaluation with histopathological examination provides a more complete understanding of endometrial dysfunction and may guide targeted management strategies such as hormonal supplementation or antimicrobial therapy.

CONCLUSION

The findings of this study indicate that endometrial abnormalities, particularly luteal phase defect, out-of-phase maturation, and chronic endometritis, are frequent in women with recurrent miscarriages. Low serum progesterone and thyroid dysfunction were significantly associated with

these histological changes. These results suggest that a combined biochemical and histopathological evaluation of the endometrium is essential for identifying underlying causes of recurrent pregnancy loss. Early diagnosis and appropriate correction of hormonal or inflammatory abnormalities may improve endometrial receptivity and pregnancy outcomes.

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