Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/05jm4t91

ENDOMETRIAL HYPERPLASIA AND ITS ASSOCIATION WITH SERUM ESTROGEN LEVELS IN WOMEN WITH RECURRENT MISCARRIAGE AND THE ROLE OF CORTICOSTEROIDS

Dr Chaman Ara[1], Dr Hina Zuhra[2], Dr Aiman Khan[3*], Dr Nadia Jabeen[4], Dr Salma Rashid Khan[5], Dr Hamayun Mumtaz[6]

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Women Medical and Dental College, Abbottabad, Pakistan
[2]Assistant Professor, Department of Obstetrics and Gynaecology, KMU Institute of Medical Sciences/Liaqat Memorial Hospital, Kohat, Pakistan
[3*]MPhil Scholar, Department of Histopathology, Khyber Medical University, Peshawar, Pakistan
[4]Associate Professor, Department of Obstetrics and Gynaecology, Rawal Institute of Health Sciences, Islamabad, Pakistan
[5]Assistant Professor, Department of Pharmacology, Women Medical and Dental College, Abbottabad, Pakistan
[6]Assistant Professor, Department of Chemical Pathology, Poonch Medical College, Rawalakot, Pakistan

***Corresponding Author:** Dr Aiman Khan,
*Mphil Scholar, Department Of Histopathology, Khyber Medical University, Peshawar, Pakistan
Email: Aiman.Khan2009@Gmail.Com

ABSTRACT

Background

Recurrent miscarriage is a distressing condition affecting many women of reproductive age, with endometrial pathology and hormonal imbalance being important contributors. Elevated serum estradiol may promote endometrial hyperplasia and impair receptivity, increasing the risk of pregnancy loss. Corticosteroid therapy has been proposed as a potential intervention to improve outcomes in selected cases.

Objective

To evaluate the association between endometrial hyperplasia and serum estradiol levels in women with recurrent miscarriage and to determine the impact of corticosteroid therapy on subsequent pregnancy outcomes.

Methods

This prospective observational study was conducted at Women Medical and Dental College, Abbottabad, from January 2023 to January 2024. A total of 73 women with a history of recurrent miscarriage were enrolled. Endometrial biopsy was performed and classified into histological subtypes. Serum estradiol levels were measured using chemiluminescent immunoassay. Women with endometrial abnormalities were offered low-dose corticosteroid therapy, and pregnancy outcomes were recorded.

Results
Endometrial hyperplasia was identified in 60.3% of participants, with complex hyperplasia being the most frequent subtype. Women with hyperplasia had significantly higher mean estradiol levels compared to those without hyperplasia (268.5 ± 42.3 pg/mL vs. 219.7 ± 38.9 pg/mL, p=0.03). Among women who conceived after corticosteroid therapy, those achieving live births had lower estradiol levels compared to those with persistent miscarriage (230.6 ± 35.4 pg/mL vs. 276.2 ± 40.7 pg/mL, p=0.02). Corticosteroid therapy improved live birth rates (65.6% vs. 29.3%, p=0.002) and reduced miscarriage recurrence (28.1% vs. 61.0%, p=0.001). Side effects such as weight gain and glucose intolerance were observed in a minority of cases.
Conclusion
Endometrial hyperplasia and elevated serum estradiol are significant risk factors for recurrent miscarriage. Corticosteroid therapy appears to enhance live birth rates in selected women, although careful monitoring is necessary. Early hormonal and endometrial assessment may guide individualized management strategies for recurrent pregnancy loss.

Keywords
Endometrial hyperplasia, Estradiol, Recurrent miscarriage, Corticosteroid therapy, Pregnancy outcome

INTRODUCTION

Recurrent miscarriage, defined as the loss of two or more consecutive pregnancies, is a distressing reproductive challenge affecting approximately 1–2% of women of childbearing age worldwide. Despite advances in reproductive medicine, the underlying cause often remains unexplained in nearly half of these cases, leaving affected couples with limited treatment options and significant psychological stress (1-3).

Among the many potential contributors, endometrial pathology has emerged as a major risk factor. The endometrium plays a central role in implantation and placental development, and hyperplastic changes may impair receptivity and disrupt the maternal–embryo interface. Histological abnormalities such as simple, complex, and atypical hyperplasia have been found more frequently in women with recurrent pregnancy loss compared to fertile controls, suggesting that abnormal tissue remodeling may predispose to pregnancy failure (4-6).

In addition to structural changes, hormonal imbalance particularly excessive estrogen exposure has been implicated in recurrent miscarriage. Estradiol is essential for follicular growth and endometrial proliferation; however, persistently elevated levels can lead to hyperplasia, impaired decidualization, and reduced implantation potential. The delicate balance between estrogen and progesterone is therefore critical for maintaining an environment conducive to pregnancy (7-10).

The present study was designed to investigate the association between endometrial hyperplasia and serum estradiol levels in women with recurrent miscarriage, and to evaluate the role of corticosteroid therapy in improving pregnancy outcomes. By combining histological assessment with hormonal evaluation, this study aims to provide a more comprehensive understanding of the factors contributing to recurrent pregnancy loss and potential therapeutic strategies.

METHODOLOGY

This prospective observational study was conducted at the Department of Obstetrics and Gynecology, Women Medical and Dental College, Abbottabad, from January 2023 to January 2024. The objective was to assess the association of endometrial hyperplasia and serum estrogen levels with recurrent miscarriage and to evaluate the role of corticosteroid therapy in improving reproductive outcomes. The study protocol was approved by the Institutional Review Committee of Women Medical and Dental College, Abbottabad. Written informed consent was obtained from all participants, and confidentiality of data was maintained throughout.

A total of 73 women with a history of recurrent miscarriage were enrolled through consecutive sampling. Recurrent miscarriage was defined as the loss of two or more consecutive pregnancies confirmed either clinically or ultrasonographically. Eligible participants were of reproductive age and had completed full medical and gynecological evaluation.

Inclusion Criteria

- Women aged 20–45 years
- History of ≥2 consecutive miscarriages
- Willingness to undergo endometrial biopsy and serum estrogen testing
- Availability for follow-up during the study period

Exclusion Criteria

- Structural uterine anomalies (e.g., septate uterus, fibroids)
- Known chromosomal abnormalities in either partner
- Infectious causes of miscarriage (TORCH infections)
- Long-term use of anticoagulant or immunosuppressive therapy prior to enrollment
- Diagnosed systemic autoimmune conditions such as systemic lupus erythematosus

After obtaining informed consent, detailed demographic and clinical information was recorded, including age, body mass index (BMI), gravidity, parity, medical comorbidities, family history, and prior gynecological interventions. The number and gestational age of miscarriages were documented. Each participant underwent endometrial sampling via biopsy or curettage. Histopathological examination was carried out in the institutional pathology department, and findings were categorized as:

- No hyperplasia
- Simple hyperplasia
- Complex hyperplasia
- Atypical hyperplasia

Venous blood samples were collected during the mid-luteal phase of the menstrual cycle to measure serum estradiol (E2) levels. Analysis was performed using a chemiluminescent immunoassay (CLIA), with results expressed in pg/mL. Laboratory reference ranges were used for interpretation. Estradiol levels were compared between groups according to endometrial findings, miscarriage history, and pregnancy outcomes.

Women with immune-mediated recurrent miscarriage or significant endometrial abnormalities were offered low-dose corticosteroid therapy (oral prednisolone). Treatment was initiated in the preconception period and continued into early gestation as clinically indicated. Women who did not receive corticosteroids served as the comparison group. Adverse effects including weight gain, hypertension, and glucose intolerance were monitored throughout therapy.

The primary outcomes were:

1. Association between endometrial hyperplasia and serum estrogen levels in women with recurrent miscarriage.
2. Effect of corticosteroid therapy on live birth rates.

Secondary outcomes included miscarriage recurrence, preterm birth, and corticosteroid-related adverse effects.

All data were entered and analyzed using SPSS version 26. Quantitative variables (age, BMI, serum estradiol levels) were presented as mean ± standard deviation (SD). Categorical variables (endometrial hyperplasia type, pregnancy outcomes) were expressed as frequencies and percentages. Independent sample t-test or ANOVA was applied to compare mean serum estrogen levels across groups. Associations between categorical variables were tested using the Chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

RESULTS

The study included 73 women with a history of recurrent miscarriage. The majority of participants were aged between 30–39 years. Most women were in the overweight BMI category, while obesity was also observed in a considerable proportion. Gravidity varied, with more than half of the participants experiencing four or more pregnancy losses.

Table 1. Demographic Profile of Participants (n=73)

Variable	Frequency (%)	p-value
Age (years)		
20–29	18 (24.7)	
30–39	41 (56.2)	
≥40	14 (19.1)	0.08
BMI (kg/m²)		
Normal (18.5–24.9)	21 (28.8)	
Overweight (25–29.9)	32 (43.8)	
Obese (≥30)	20 (27.4)	0.12
Gravidity		
2–3	26 (35.6)	
≥4	47 (64.4)	0.04*

*Significant at $p<0.05$

Endometrial hyperplasia was identified in a substantial proportion of women, with complex hyperplasia being the most frequent subtype. Atypical hyperplasia was less common but still clinically relevant. Comorbidities such as hypertension, diabetes, and thyroid disorders were also reported among the study population.

Table 2. Clinical and Endometrial Findings

Variable	Frequency (%)	p-value
Endometrial Hyperplasia Type		
No hyperplasia	29 (39.7)	
Simple hyperplasia	18 (24.7)	
Complex hyperplasia	20 (27.4)	
Atypical hyperplasia	6 (8.2)	0.03*
Comorbidities		
Hypertension	11 (15.1)	
Diabetes mellitus	8 (11.0)	
Thyroid disorder	10 (13.7)	0.21

*Significant at $p<0.05$

Serum estradiol (E2) levels were measured in all participants. Women with endometrial hyperplasia demonstrated significantly higher mean estradiol levels compared to women without hyperplasia. Moreover, women who achieved live births after corticosteroid therapy showed comparatively balanced estradiol levels, while persistently elevated levels were observed in those who continued to miscarry.

Table 3. Serum Estradiol Levels in Study Participants (n=73)

Group	Mean ± SD (pg/mL)	p-value
Women with hyperplasia (n=44)	**268.5 ± 42.3**	
Women without hyperplasia (n=29)	**219.7 ± 38.9**	0.03*
Live birth (after corticosteroid)	**230.6 ± 35.4**	
Miscarriage (after corticosteroid)	**276.2 ± 40.7**	0.02*

*Significant at $p<0.05$

Corticosteroid therapy was administered to women with immune-mediated recurrent miscarriage or significant endometrial abnormalities. Pregnancy outcomes were significantly better in the treated group, with higher live birth rates and lower miscarriage recurrence compared to untreated women. Adverse effects of corticosteroid therapy, including weight gain and glucose intolerance, were noted in a minority of participants.

Table 4. Corticosteroid Therapy and Pregnancy Outcomes

Outcome After Corticosteroid Use	With Steroids (n=32)	Without Steroids (n=41)	p-value
Live birth achieved	21 (65.6)	12 (29.3)	0.002*
Miscarriage continued	9 (28.1)	25 (61.0)	0.001*
Preterm birth	2 (6.3)	3 (7.3)	0.82
Adverse effects noted	5 (15.6)	–	–

*Significant at $p<0.05$

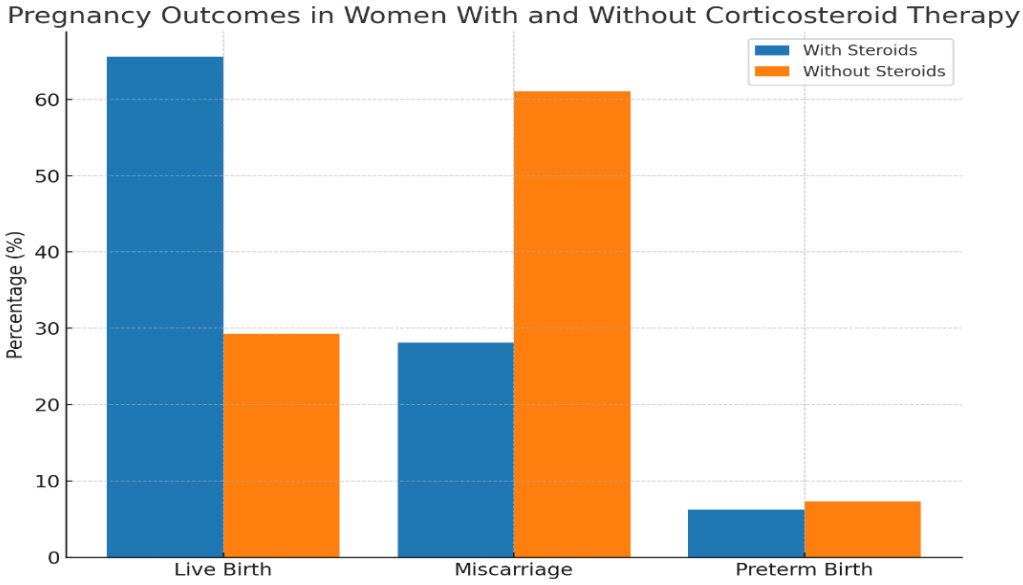

FIGURE 1

Bar graph showing pregnancy outcomes in women with and without corticosteroid therapy. The live birth rate was higher and miscarriage rate lower in those receiving corticosteroids.

DISCUSSION

This study highlights the strong association between endometrial hyperplasia, elevated serum estradiol levels, and recurrent miscarriage. Nearly two-thirds of the women in our cohort demonstrated endometrial abnormalities, with complex hyperplasia being the most common subtype. These findings support previous reports that altered endometrial architecture disrupts implantation and early placental development, predisposing women to pregnancy loss. Abnormal proliferation and reduced receptivity of the endometrium have been described as important contributors to recurrent miscarriage, particularly in women with repeated implantation failure (11-13).

Our study also demonstrated that women with endometrial hyperplasia had significantly higher serum estradiol levels compared to those with normal endometrial histology. Excessive estrogen exposure is known to promote endometrial proliferation, disturb the balance between estrogen and progesterone, and impair decidualization. These hormonal disturbances may compromise endometrial receptivity, leading to recurrent pregnancy loss. Consistent with our findings, earlier studies have reported that hyperestrogenism correlates with aberrant endometrial changes and adverse reproductive outcomes (14).

Importantly, when outcomes were analyzed in relation to subsequent pregnancies, women who achieved live births following corticosteroid therapy tended to have more balanced estradiol levels, whereas those with persistent miscarriage had significantly higher values. This observation suggests that abnormal estrogen dynamics may contribute not only to the development of endometrial hyperplasia but also to the failure of pregnancy continuation. Corticosteroids, by reducing endometrial inflammation and modulating the immune environment, may indirectly improve the estrogen–progesterone balance at the maternal–fetal interface (15)

The beneficial role of corticosteroid therapy observed in this study further supports its selective use in women with recurrent miscarriage. Those who received prednisolone had markedly improved live birth rates compared to untreated women. These findings are consistent with existing literature where corticosteroid therapy, through its immunomodulatory action, has been shown to enhance implantation success and reduce pregnancy loss in women with reproductive immunological abnormalities. Nevertheless, the occurrence of side effects such as weight gain and glucose intolerance in our cohort underlines the need for careful monitoring and patient selection(16-18). Overall, this study underscores the multifactorial nature of recurrent miscarriage, where structural endometrial abnormalities, hormonal imbalance, and immune dysregulation interact to compromise pregnancy maintenance. By integrating histopathological assessment, hormonal profiling, and selective immunomodulatory therapy, clinicians can better identify at-risk women and optimize reproductive outcomes (19, 20).

CONCLUSION

This study demonstrates that endometrial hyperplasia and elevated serum estradiol levels are significant risk factors for recurrent miscarriage. Women with hyperplastic endometrium had higher estradiol concentrations compared to those with normal endometrium, highlighting the impact of hormonal imbalance on reproductive failure. Corticosteroid therapy significantly improved live birth rates in women with recurrent miscarriage and endometrial abnormalities, although some adverse effects were noted.

REFERENCES

1. La Marca A, Mastellari E. Infertility: Epidemiology and etiology. Female reproductive dysfunction: Springer; 2020. p. 1-23.
2. Palshetkar N, Palshetkar R, Kannan J, Pai HD, Ayyavoo C. Handbook of Recurrent Pregnancy Loss: Jaypee Brothers Medical Publishers; 2020.
3. Ali R, Khan TA, Gul H, Rehman RJC. An interplay of Progesterone, Leukemia Inhibitor Factor and Interleukin-6 in the window of implantation; Impact on fertility. 2023;170:156332.
4. Al-Lamee H, Hill CJ, Turner F, Phan T, Drakeley AJ, Hapangama DK, et al. The role of endometrial stem/progenitor cells in recurrent reproductive failure. 2022;12(5):775.
5. Wyrwoll MJ, Rudnik-Schöneborn S, Tüttelmann FJMG. Genetic counseling and diagnostic guidelines for couples with infertility and/or recurrent miscarriage. 2021;33(1):3-12.
6. Cope DI, Monsivais DJC. Progesterone receptor signaling in the uterus is essential for pregnancy success. 2022;11(9):1474.
7. Maurya VK, DeMayo FJ, Lydon JPJFiC, Biology D. Illuminating the “black box” of progesterone-dependent embryo implantation using engineered mice. 2021;9:640907.

8. Tsakiridis I, Giouleka S, Koutsouki G, Kostakis N, Kalogiannidis I, Kourtis A, et al. Investigation and management of abnormal uterine bleeding in reproductive-aged women: a descriptive review of national and international recommendations. 2022;27(6):504-17.
9. Zagouri F, Dedes N, Papatheodoridi A, Liontos M, Dimopoulos MAJBP, Childbirth. Supportive medication in cancer during pregnancy. 2020;20(1):747.
10. Moreno I, Capalbo A, Mas A, Garrido-Gomez T, Roson B, Poli M, et al. The human periconceptional maternal-embryonic space in health and disease. 2023;103(3):1965-2038.
11. Agcaoili-De Jesus MSL, Alentajan-Aleta LTC, Ocampo-Cervantes CC, Otadoy-Agustin JR, Kwak-Kim J. Mast cell pathology and reproductive failures. Immunology of Recurrent Pregnancy Loss and Implantation Failure: Elsevier; 2022. p. 71-92.
12. Maurya VK, Szwarc MM, Lonard DM, Gibbons WE, Wu S-P, O'Malley BW, et al. Decidualization of human endometrial stromal cells requires steroid receptor coactivator-3. 2022;4:1033581.
13. Sarkar M, Brady CW, Fleckenstein J, Forde KA, Khungar V, Molleston JP, et al. Reproductive health and liver disease: practice guidance by the American Association for the Study of Liver Diseases. 2021;73(1):318-65.
14. Khouri H, Hasan MEJE, Med MSJ. Overview of Female Infertility: Causes. 2023;12:1319-32.
15. Equils O, Kellogg C, McGregor J, Gravett M, Neal-Perry G, Gabay CJBor. The role of the IL-1 system in pregnancy and the use of IL-1 system markers to identify women at risk for pregnancy complications. 2020;103(4):684-94.
16. Qamar AY, Hussain T, Rafique MK, Bang S, Tanga BM, Seong G, et al. The role of stem cells and their derived extracellular vesicles in restoring female and male fertility. 2021;10(9):2460.
17. DeMayo FJ, Lydon JPJJome. 90 YEARS OF PROGESTERONE: New insights into progesterone receptor signaling in the endometrium required for embryo implantation. 2020;65(1):T1-T14.
18. Allen RHJU, Waltham, MA. Combined estrogen-progestin oral contraceptives: patient selection, counseling, and use. 2023.
19. Bakkensen JB, Agarwal R, Shapiro MJCO, Reports G. Recent advances and current perspectives on endometrial receptivity. 2021;10(4):45-52.
20. Romanenko TH, Haiduk AD, Turbanist SVJWL. A STATISTICAL ANALYSIS OF WOMEN'S REPRODUCTIVE HEALTH CHARACTERISTICS AFTER INEFFECTIVE REATTEMPTS OF USING ART. 2021;74(4):940-7.