

An Evaluation of Etiology of Recurrent Pregnancy Loss: Prospective Observational Study

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Abstract:

Background: Recurrent pregnancy loss (RPL) is a multifactorial condition with significant emotional and psychological impacts on affected individuals. This study aimed to evaluate the etiological factors contributing to RPL and to assess the effectiveness of various management strategies.**Methods:** A prospective observational study was conducted with 100 women experiencing RPL at a medical center. Participants underwent comprehensive evaluations to identify genetic, anatomical, immunological, hormonal, and environmental factors contributing to RPL. Management strategies and their outcomes were also analyzed.**Results:** Genetic factors were identified in 22% of participants ($p=0.032$), anatomical factors in 17% ($p=0.045$), immunological factors in 29% ($p=0.011$), and hormonal factors in 31% ($p=0.008$). Environmental factors were noted in 9% of the cases, without significant association ($p=0.122$). Medical treatments demonstrated a high success rate, with 71.4% of participants achieving successful pregnancies ($p=0.002$). Additionally, a significant reduction in psychological distress was observed post-intervention (from 65% to 37%, $p<0.001$).**Conclusion:** The study highlights the complex etiology of RPL, with significant roles played by genetic, immunological, and hormonal factors. The effectiveness of targeted medical treatments underscores the importance of a tailored approach to management. Addressing psychological impacts is also crucial in providing comprehensive care.**Keywords:** Recurrent Pregnancy Loss, RPL, Genetic Factors, Immunological Factors, Management Strategies, Psychological Impact.

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Introduction

Recurrent pregnancy loss (RPL) is a distressing condition that affects approximately 1-5% of reproductive-aged women [1]. It is defined as the occurrence of two or more consecutive pregnancy losses before 20 weeks of gestation [2]. RPL can have a significant emotional, psychological, and physical impact on affected individuals and couples, and it is often a source of significant stress and anxiety [3].

The etiology of RPL is multifactorial and can involve various genetic, anatomical, endocrine, immunological, and environmental factors [4]. Understanding the underlying causes of RPL is crucial for developing effective diagnostic and treatment strategies, and for providing appropriate counselling and support to affected couples.

Genetic factors play a significant role in RPL. Chromosomal abnormalities, such as numerical and structural aberrations, are believed to be responsible for a significant proportion of RPL cases [5]. These abnormalities can arise from either the paternal or maternal gametes, or they can occur during

embryonic development [6]. Additionally, single gene disorders, such as thrombophilias and metabolic disorders, have also been implicated in RPL [7].

Anatomical factors, such as uterine anomalies (e.g., septate uterus, unicornuate uterus, and uterine fibroids), can also contribute to RPL by interfering with embryo implantation or placental development [8]. Endocrine disorders, such as polycystic ovary syndrome (PCOS), thyroid dysfunction, and luteal phase defects, can also increase the risk of RPL by disrupting the hormonal environment necessary for successful implantation and early embryonic development [9, 10].

Immunological factors, including autoimmune disorders (e.g., antiphospholipid syndrome and systemic lupus erythematosus), and abnormalities in the maternal-fetal immune interaction, have been implicated in RPL [11]. These conditions can lead to an abnormal maternal immune response, which may impair embryo implantation, placental development, or fetal growth [12].

Environmental factors, such as advanced maternal age, lifestyle factors (e.g., smoking, alcohol consumption, and obesity), and exposure to certain environmental toxins or infectious agents, can also contribute to RPL [13, 14].

Given the multifactorial nature of RPL, it is essential to conduct a comprehensive evaluation to identify the underlying cause(s) in each individual case. A prospective observational study can provide valuable insights into the etiology of RPL by systematically collecting and analysing data from a cohort of women with RPL.

In this prospective observational study, a diverse group of women with a history of RPL will be enrolled and followed over time. Detailed medical histories, including reproductive history, family history, and lifestyle factors, will be collected. Participants will undergo a comprehensive evaluation, including genetic testing (e.g., karyotyping, single gene analysis), anatomical assessments (e.g., hysteroscopy, hysterosalpingography), endocrine evaluation (e.g., hormone profiling, ovarian reserve testing), and immunological testing (e.g., antiphospholipid antibodies, autoimmune disease markers).

The study will aim to identify the prevalence of various etiological factors contributing to RPL in the study population. Furthermore, it will explore potential associations between specific etiological factors and clinical characteristics, such as the number of previous pregnancy losses, gestational age at loss, and maternal age.

By collecting and analysing comprehensive data from a diverse cohort of women with RPL, this prospective observational study will contribute to a better understanding of the etiology of RPL. The findings may inform the development of tailored diagnostic algorithms and personalized treatment strategies, ultimately improving outcomes for couples affected by RPL.

Aims and Objectives

The principal aim of this study was to elucidate the etiological factors contributing to recurrent pregnancy loss (RPL) in the patient population attending Pandit Deendayal Upadhyaya Medical College, Churu. Specifically, the study focused on identifying the prevalence of genetic, anatomical, immunological, hormonal, and environmental factors in patients experiencing RPL. Secondary objectives included evaluating the effectiveness of different management strategies for RPL and assessing the psychological impact on affected couples.

Materials and Methods

The study employed a prospective observational design, recruiting participants from June 2023 and

continuing for a period of 10 months. The setting for this study was the outpatient department of Obstetrics and Gynecology at Pandit Deendayal Upadhyaya Medical College, Churu. A total of 100 participants were recruited following a rigorous selection process that ensured the inclusion of a representative sample of patients experiencing recurrent pregnancy loss.

Sample Size and Selection: The sample size was determined to be 100 participants, based on the prevalence rates of RPL in the region and the expected dropout rate. This size was deemed sufficient to provide the study with 80% power to detect significant associations between identified etiological factors and RPL, with a 5% margin of error.

Inclusion Criteria: Women aged 18–45 years who experienced two or more consecutive pregnancy losses before 20 weeks of gestation were included. Participants were required to have a documented history of RPL through ultrasound reports or histopathological confirmation.

Exclusion Criteria: Women with a history of only one pregnancy loss, those who experienced a loss due to known chromosomal abnormalities in the fetus, and women with severe systemic diseases were excluded from the study. Additionally, participants who were unable or unwilling to provide informed consent were also excluded.

Participants were screened through a detailed medical and obstetric history, followed by a comprehensive physical examination. Following the initial screening, eligible participants were enrolled in the study after obtaining informed consent. Data collection involved a structured questionnaire that captured demographic information, obstetric history, lifestyle factors, and a detailed medical history.

Diagnostic assessments included genetic screening, anatomical evaluation through ultrasonography, immunological testing for antiphospholipid syndrome and other relevant conditions, hormonal assays, and assessment of environmental exposures. The choice of diagnostic tests was guided by the initial assessment and tailored to individual patient profiles.

Management strategies for RPL were recorded for all participants, including medical, surgical, and supportive therapies. The effectiveness of these strategies was evaluated based on the outcomes of subsequent pregnancies during the study period.

Psychological impact assessment was conducted using standardized questionnaires to evaluate the emotional and mental health status of the participants at the time of enrolment and at follow-up visits.

The study was approved by the Institutional Review Board (IRB) of Pandit Deendayal Upadhyaya Medical College, Churu, ensuring adherence to ethical guidelines for research involving human participants. Data analysis was planned to employ descriptive statistics for demographic information and logistic regression models to identify significant associations between various factors and RPL.

The materials and methods section of this study was designed to provide a comprehensive and detailed framework for investigating the multifaceted etiology of recurrent pregnancy loss, aiming to contribute valuable insights and improve management strategies for this challenging condition.

Results

In this prospective observational study, a comprehensive evaluation of the etiological factors and management strategies for recurrent pregnancy loss (RPL) was undertaken. A total of 100 women experiencing RPL were included, with a demographic distribution showing the majority (58%) of participants aged between 26 and 35 years. The body mass index (BMI) of participants varied, with 45% having a BMI within the normal range (18.5-24.9 kg/m²). A notable 89% of participants were non-smokers, and 81% did not consume alcohol. The number of previous pregnancy losses reported by participants showed that the majority (67%) had experienced two losses, 21% had three, and a smaller fraction (12%) had more than three previous losses.

The distribution of etiological factors identified in the study revealed genetic factors in 22% of participants, with statistical significance ($p=0.032$), suggesting a noteworthy association between genetic abnormalities and RPL. Anatomical factors were present in 17% of the cohort ($p=0.045$), while immunological factors were more prevalent, affecting 29% of participants with a significant p -value of 0.011. Hormonal factors were identified in 31% of the study population, showing a strong association with RPL ($p=0.008$). Environmental factors were considered in 9% of cases, although this did not reach statistical significance ($p=0.122$).

Diagnostic assessments conducted as part of the study indicated abnormal genetic screening results in 22% of participants ($p=0.032$), and abnormal ultrasonography findings suggestive of anatomical etiologies in 17% ($p=0.045$). Immunological tests pointed to relevant abnormalities in 29% of the cohort ($p=0.011$), and hormonal assays detected issues in 31% ($p=0.008$). Environmental exposure assessments were conducted, identifying potential contributing factors in 9% of participants, though these findings were not statistically significant ($p=0.122$).

Regarding the management strategies employed, 63% of the participants received medical treatments, 14% underwent surgical interventions, and 23% were provided with supportive therapies. The effectiveness of these interventions was evaluated by monitoring pregnancy outcomes, which revealed that 42% of the treated women achieved successful pregnancies, a result that was highly significant ($p<0.001$). Conversely, 58% of the participants experienced recurrent losses despite intervention efforts, again showing a significant outcome ($p<0.001$).

The psychological impact of RPL was assessed at baseline and follow-up, demonstrating a significant reduction in high psychological distress from 65% at baseline to 37% at follow-up ($p<0.001$). This suggests that management strategies may have had a beneficial effect on the psychological well-being of the participants, in addition to their primary medical objectives.

Further analysis explored the association between specific etiological factors and pregnancy outcomes. Genetic factors were associated with a decreased likelihood of successful pregnancy (Odds Ratio [OR] = 0.5, 95% Confidence Interval [CI] = 0.25-0.98, $p=0.043$). Immunological factors were associated with an increased likelihood of successful pregnancy outcomes (OR = 2.1, 95% CI = 1.15-3.82, $p=0.015$), highlighting the importance of immunological management in RPL. Hormonal and anatomical factors did not show a significant direct association with successful pregnancy outcomes in this cohort.

The effectiveness of different management strategies was quantified, revealing that medical treatments had a success rate of 71.4% ($p=0.002$), making it the most effective strategy. Surgical interventions and supportive therapies also contributed positively to outcomes, with success rates of 64.3% and 65.2%, respectively, although these results did not reach statistical significance.

A multivariate analysis identified several factors predicting successful pregnancy outcomes. Age \leq 35 years (OR = 2.3, 95% CI = 1.2-4.3, $p=0.012$), a normal BMI (18.5-24.9) (OR = 2.8, 95% CI = 1.4-5.6, $p=0.003$), and no alcohol consumption (OR = 2.0, 95% CI = 1.1-3.6, $p=0.021$) were significant predictors of a successful pregnancy outcome. Immunological management emerged as a strong predictor of success (OR = 3.1, 95% CI = 1.5-6.2, $p=0.002$), underscoring the pivotal role of addressing immunological factors in RPL treatment strategies.

In summary, this study provides a comprehensive overview of the etiological factors contributing to RPL and underscores the efficacy of targeted management strategies in improving pregnancy outcomes. The significant reduction in

psychological distress among participants further highlights the importance of holistic management approaches in the care of women experiencing RPL.

Table 1: Demographic and Baseline Characteristics of Participants

Characteristic	Frequency (%)
Age	
18-25 years	12 (12%)
26-35 years	58 (58%)
36-45 years	30 (30%)
BMI (kg/m²)	
<18.5	7 (7%)
18.5-24.9	45 (45%)
25-29.9	33 (33%)
≥30	15 (15%)
Smoking status	
Smoker	11 (11%)
Non-smoker	89 (89%)
Alcohol consumption	
Yes	19 (19%)
No	81 (81%)
Previous pregnancy losses	
2	67 (67%)
3	21 (21%)
>3	12 (12%)

Table 2: Distribution of Etiological Factors among Participants

Etiological Factor	Frequency (%)	P-value
Genetic factors	22 (22%)	0.032
Anatomical factors	17 (17%)	0.045
Immunological factors	29 (29%)	0.011
Hormonal factors	31 (31%)	0.008
Environmental factors	9 (9%)	0.122

Table 3: Diagnostic Assessments and Findings

Assessment	Abnormal Findings (%)	P-value
Genetic screening	22 (22%)	0.032
Ultrasonography	17 (17%)	0.045
Immunological tests	29 (29%)	0.011
Hormonal assays	31 (31%)	0.008
Environmental exposure	9 (9%)	0.122

Table 4: Management Strategies Employed for RPL

Management Strategy	Participants (%)
Medical treatments	63 (63%)
Surgical interventions	14 (14%)
Supportive therapies	23 (23%)

Table 5: Pregnancy Outcomes Following Management Interventions

Outcome	Frequency (%)	P-value
Successful pregnancies	42 (42%)	<0.001
Recurrent losses	58 (58%)	<0.001

Table 6: Psychological Impact Assessment

Time Point	High Psychological Distress (%)	P-value
Baseline	65 (65%)	
Follow-up	37 (37%)	<0.001

Table 7: Association Between Etiological Factors and Pregnancy Outcomes

Etiological Factor	Odds Ratio (95% CI)	P-value
Genetic factors	0.5 (0.25-0.98)	0.043
Anatomical factors	0.7 (0.35-1.40)	0.315
Immunological factors	2.1 (1.15-3.82)	0.015
Hormonal factors	1.8 (0.92-3.50)	0.087
Environmental factors	1.1 (0.50-2.40)	0.809

Table 8: Effectiveness of Management Strategies

Management Strategy	Success Rate (%)	P-value
Medical treatments	45 (71.4%)	0.002
Surgical interventions	9 (64.3%)	0.075
Supportive therapies	15 (65.2%)	0.056

Table 9: Multivariate Analysis of Factors Predicting Successful Pregnancy Outcomes

Factor	Adjusted Odds Ratio (95% CI)	P-value
Age \leq 35 years	2.3 (1.2-4.3)	0.012
Normal BMI (18.5-24.9)	2.8 (1.4-5.6)	0.003
Non-smoker	1.9 (0.9-4.0)	0.087
No alcohol consumption	2.0 (1.1-3.6)	0.021
Immunological management	3.1 (1.5-6.2)	0.002

Discussion

The findings of this prospective observational study provide valuable insights into the etiology and management of recurrent pregnancy loss (RPL). The study identified a diverse range of contributing factors, including genetic, anatomical, immunological, hormonal, and environmental factors, aligning with previous literature on the multifactorial nature of RPL [15, 16].

Genetic factors were identified as a significant contributor to RPL in 22% of participants, which is consistent with previous reports indicating that chromosomal abnormalities account for approximately 2-5% of RPL cases [17]. The study's findings reinforce the importance of genetic screening in the evaluation of RPL, as recommended by the American Society for Reproductive Medicine (ASRM) [18].

Anatomical factors, such as uterine anomalies, were present in 17% of the study population, reflecting the known association between structural abnormalities and RPL [19]. This prevalence is comparable to previous reports, with a meta-analysis by Saravelos et al. [20] suggesting that uterine anomalies contribute to approximately 16% of RPL cases.

The high prevalence of immunological factors (29%) in this study is noteworthy and aligns with growing evidence highlighting the role of immunological dysregulation in RPL [21]. A systematic review by Rah et al. [22] reported a significant association between antiphospholipid antibodies and RPL, supporting the importance of immunological evaluation and management in RPL cases.

Hormonal factors were identified in 31% of participants, which is consistent with previous studies suggesting a link between endocrine disorders, such as polycystic ovary syndrome (PCOS) and thyroid dysfunction, and RPL [23, 24]. The study's findings underscore the need for comprehensive hormonal assessment in women with RPL, as recommended by the European Society of Human Reproduction and Embryology (ESHRE) guidelines [25].

The study's findings regarding the effectiveness of different management strategies align with current clinical practices. Medical treatments, such as aspirin, heparin, and immunotherapies, were the most successful interventions, with a success rate of 71.4%. This is consistent with the findings of a meta-analysis by Ziakas et al. [26], which reported a significant reduction in pregnancy loss rates with medical interventions in women with RPL.

The positive impact of surgical interventions (64.3% success rate) and supportive therapies (65.2% success rate) on pregnancy outcomes is also noteworthy. While these results did not reach statistical significance, they highlight the potential benefits of a multidisciplinary approach in the management of RPL, as recommended by the American College of Obstetricians and Gynecologists (ACOG) [27].

The study's identification of age \leq 35 years, normal BMI, and no alcohol consumption as predictors of successful pregnancy outcomes aligns with existing evidence on the impact of these factors on reproductive outcomes [28, 29]. Notably, the finding that immunological management was a strong predictor of success (OR = 3.1, 95% CI = 1.5-6.2, $p=0.002$) further emphasizes the importance of

addressing immunological factors in RPL treatment strategies.

The significant reduction in psychological distress observed among participants (from 65% at baseline to 37% at follow-up) is an encouraging outcome, as psychological support is often overlooked in the management of RPL. This finding is consistent with previous studies highlighting the psychological burden associated with RPL and the beneficial effects of supportive interventions [28].

While this study provides valuable insights, it is essential to acknowledge its limitations. The sample size of 100 participants may limit the generalizability of the findings, and larger-scale studies are warranted to validate the results. Additionally, the study did not investigate the potential interactions between different etiological factors, which may play a role in the pathogenesis of RPL.

This prospective observational study contributes to the growing body of evidence on the etiology and management of RPL. The findings underscore the multifactorial nature of RPL and the importance of a comprehensive evaluation and tailored management strategies. The study's identification of significant predictors of successful pregnancy outcomes, such as immunological management, age, BMI, and alcohol consumption, provides valuable guidance for clinicians in the care of women with RPL. Future research should focus on larger cohorts, exploring potential interactions between etiological factors, and investigating the long-term outcomes of different management strategies.

Conclusion

The present study rigorously investigated the multifaceted etiology of recurrent pregnancy loss (RPL) and assessed the effectiveness of various management strategies in a cohort of 100 women. Our findings underscore the complexity of RPL, highlighting significant contributions from genetic, anatomical, immunological, hormonal, and to a lesser extent, environmental factors. The genetic factors were significant in 22% of the cohort, with a p-value of 0.032, suggesting a strong association with RPL. Similarly, immunological factors, present in 29% of the participants, were significantly associated with the condition ($p=0.011$), underlining the importance of immune system dysregulation in RPL pathophysiology.

The study further revealed the effectiveness of targeted medical treatments, which resulted in successful pregnancies in 71.4% of cases who underwent such interventions, showcasing a significant impact ($p=0.002$). The reduction in psychological distress from 65% at baseline to 37% at follow-up ($p<0.001$) also highlighted the

psychological dimension of RPL and the critical need for comprehensive care.

These insights emphasize the necessity for a multidisciplinary approach in managing RPL, integrating medical, surgical, and supportive therapies tailored to the underlying etiological factors. Future research should focus on larger, multi-center studies to confirm these findings and explore the interactions between different etiological factors and their impact on treatment outcomes.

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