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RISK FACTORS ASSOCIATED WITH PREGNANCY OUTCOMES IN PATIENTS WITH RECURRENT PREGNANCY LOSS AFTER TREATMENT IN FETOMATERNAL MEDICINE DEPARTMENT, BSMMU, DHAKA, BANGLADESH

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KEYWORDS

Recurrent pregnancy loss; Pregnancy outcome; Risk factors; Bangladesh; Antiphospholipid syndrome; Fetomaternal medicine

ABSTRACT:

Background: Recurrent pregnancy loss (RPL) affects 1-5% of reproductive-age couples worldwide and causes significant psychological distress. Limited data exists regarding RPL management and outcomes in South Asian populations, particularly in resource-constrained settings such as Bangladesh.
Objective: To investigate risk factors associated with pregnancy outcomes in patients with recurrent pregnancy loss following treatment at the Fetomaternal Medicine Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
Methods: This prospective observational study enrolled 100 women with RPL (≥2 consecutive pregnancy losses) who received treatment at the Fetomaternal Medicine Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh between January 2023 and December 2023. Participants underwent comprehensive evaluation for potential etiological factors and received appropriate treatment based on identified causes. They were followed through conception and subsequent pregnancy. Primary outcome was live birth rate, while secondary outcomes included miscarriage, stillbirth, and obstetric complications. Univariate and multivariate analyses were performed to identify factors associated with adverse pregnancy outcomes.
Results: Identifiable causes of RPL were found in 73% of patients, with endocrine disorders (42%), anatomical factors (24%), and antiphospholipid syndrome (18%) being most prevalent. Of 100 women enrolled, 87 conceived

during the study period, with 61 (70.1%) achieving live birth. Obstetric complications occurred in a substantial proportion, including preterm delivery (23.0%), gestational diabetes (19.7%), and preeclampsia (14.8%). Multivariate analysis identified four independent risk factors for adverse pregnancy outcomes: maternal age ≥35 years (adjusted OR 4.82, 95% CI 1.17-19.88), obesity (adjusted OR 4.37, 95% CI 1.18-16.21), ≥4 previous pregnancy losses (adjusted OR 2.95, 95% CI 1.06-8.21), and antiphospholipid syndrome (adjusted OR 7.14, 95% CI 1.82-28.03). The highest live birth rates were observed in women with anatomical factors (83.3%) and endocrine disorders (76.5%), while patients with antiphospholipid syndrome (57.1%) and chromosomal abnormalities (33.3%) had poorer outcomes despite treatment.

Conclusion: Systematic evaluation can identify causative factors in a majority of RPL cases in Bangladesh, and appropriate management yields favorable outcomes in most patients. Advanced maternal age, obesity, higher number of previous losses, and antiphospholipid syndrome emerged as significant predictors of adverse outcomes. Women with previous RPL remain at increased risk for obstetric complications despite successful conception, necessitating vigilant antenatal care. These findings can guide risk stratification, personalized counseling, and resource allocation in the management of RPL in resource-constrained settings.

INTRODUCTION

Recurrent pregnancy loss (RPL), defined as two or more consecutive pregnancy losses before 24 weeks of gestation, represents a significant challenge in reproductive medicine affecting approximately 1-5% of couples attempting to conceive.[1,2] This condition imposes substantial psychological distress, frequently manifesting as anxiety, depression, and diminished quality of life among affected individuals and couples.[3] The etiology of RPL is multifactorial, with identifiable causes including chromosomal abnormalities, uterine anatomical defects, endocrine disorders, antiphospholipid syndrome, thrombophilias, immunological factors, and environmental exposures.[4,5] However, despite extensive investigation, approximately 50% of RPL cases remain unexplained, presenting significant diagnostic and therapeutic challenges.[6]Bangladesh, as a developing country with limited healthcare resources, faces unique challenges in the management of RPL. The prevalence of RPL in Bangladesh has been reported to be higher than global averages, with estimates ranging from 4.6% to 7.8% among women of reproductive age. [7,8] This increased prevalence may be attributed to various factors, including higher rates of consanguineous marriages, nutritional deficiencies, limited access to specialized healthcare services, and greater exposure to environmental toxins.[9]Bangabandhu Sheikh Mujib Medical University (BSMMU) is the premier tertiary care and academic medical institution in Bangladesh, with its Fetomaternal Medicine Department serving as a national referral center for complex obstetric cases, including RPL. The department employs a multidisciplinary approach to the evaluation and management of RPL, incorporating contemporary diagnostic modalities and treatment protocols adapted to local resource constraints.[10]Several international guidelines have been established for the management of RPL, including those by the European Society of Human Reproduction and Embryology (ESHRE), the American Society for Reproductive Medicine (ASRM), and the Royal College of Obstetricians and Gynaecologists (RCOG).[11,12,13] However, the applicability of these guidelines in resource-limited settings like Bangladesh remains uncertain. The effectiveness of various therapeutic interventions for RPL—including aspirin, heparin, progesterone, intravenous immunoglobulin, and pre-implantation genetic testing—continues to be debated, with variable evidence regarding their efficacy. [14,15] Understanding the risk factors associated with pregnancy outcomes following RPL treatment is crucial for optimizing clinical care, patient counseling, and resource allocation. Previous studies have identified maternal age, number of previous losses, presence of polycystic ovary syndrome (PCOS), thyroid dysfunction, and uterine anomalies as potential predictors of subsequent pregnancy outcomes. [16,17] However, comprehensive data from South Asian

populations, particularly from Bangladesh, remain limited, creating a significant knowledge gap in this field.The present study aims to address this gap by investigating the risk factors associated with pregnancy outcomes in 100 patients with RPL who received treatment at the Fetomaternal Medicine Department of BSMMU in Dhaka, Bangladesh. By identifying the demographic, clinical, and laboratory parameters that influence pregnancy outcomes in this cohort, we seek to enhance prognostic accuracy, refine treatment approaches, and ultimately improve care for women with RPL in Bangladesh and similar resource-constrained settings.

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study enrolled 100 women with RPL (≥2 consecutive pregnancy losses) who received treatment at the Fetomaternal Medicine Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh between January 2023 and December 2023. BSMMU serves as the national referral center for complex obstetric cases, receiving patients from across the country. The study protocol was approved by the Institutional Review Board of BSMMU and written informed consent was obtained from all participants prior to enrollment.

Study Population

One hundred consecutive patients with recurrent pregnancy loss (RPL) who fulfilled the inclusion criteria were enrolled in the study. RPL was defined according to the European Society of Human Reproduction and Embryology (ESHRE) guidelines as two or more pregnancy losses before 24 weeks of gestation. The inclusion criteria were: (1) history of two or more consecutive pregnancy losses; (2) reproductive age (18-40 years); (3) willingness to conceive; and (4) consent to participate in the study. Exclusion criteria included: (1) women with primary infertility; (2) unwillingness to conceive during the study period; (3) presence of severe medical disorders contraindicating pregnancy; and (4) lost to follow-up before conception or pregnancy outcome determination.
investigation

Data Collection and Evaluation Protocol

Upon enrollment, a comprehensive evaluation was performed for all participants according to a standardized protocol established by the department, which was adapted from international guidelines. Detailed medical, obstetric, and family histories were obtained using a structured questionnaire. Physical examination included general, systemic, and gynecological evaluations. Anthropometric measurements were recorded, and body mass index (BMI) was calculated. Laboratory investigations included complete blood count, fasting blood glucose, oral glucose tolerance test, thyroid function tests (free T3, free T4, TSH), prolactin levels, and tests for antiphospholipid syndrome (lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein-I antibodies). Thrombophilia screening (protein C, protein S, antithrombin III, Factor V Leiden, and prothrombin gene mutation) was performed in selected cases with personal or family history of thrombosis. Parental karyotyping was performed for couples with three or more pregnancy losses or a history of chromosomal abnormalities. Imaging studies included transvaginal ultrasonography to assess uterine morphology, endometrial thickness, and ovarian features. Three-dimensional ultrasonography and/or hysteroscopy were performed when conventional ultrasonography suggested uterine anomalies. Magnetic resonance imaging (MRI) was utilized in selected cases for further evaluation of complex uterine anomalies.

Treatment Protocol

Treatment was individualized based on identified etiological factors, following departmental protocols adapted from international guidelines. Patients with uterine septum underwent hysteroscopic metroplasty. Hormonal abnormalities were corrected with appropriate medications: levothyroxine for hypothyroidism, cabergoline for hyperprolactinemia, and metformin and/or clomiphene citrate for polycystic ovary syndrome (PCOS). Antiphospholipid syndrome was treated with low-dose aspirin (75-

100 mg daily) and low-molecular-weight heparin (enoxaparin 40 mg subcutaneously daily). Inherited thrombophilias were managed with low-molecular-weight heparin according to risk stratification. Women with unexplained RPL received empirical treatments based on departmental protocols, which included progesterone supplementation (vaginal micronized progesterone 200 mg twice daily) from ovulation until 12 weeks of gestation, and folic acid supplementation (5 mg daily). Low-dose aspirin was prescribed for selected cases with unexplained RPL who had evidence of impaired uterine perfusion on Doppler studies. Patients were advised to attempt conception following the completion of diagnostic workup and implementation of appropriate interventions. Pre-conception counseling was provided regarding optimal timing of intercourse, lifestyle modifications, and stress reduction techniques.

Follow-up and Outcome Assessment

Participants were followed up monthly during the pre-conception period and more frequently (every 2-4 weeks) following conception. Upon confirmation of pregnancy, close antenatal surveillance was instituted, with serial ultrasonography for viability, growth assessment, and fetal well-being. Additional monitoring was implemented based on specific risk factors and complications. The primary outcome was live birth, defined as delivery of a viable infant after 24 weeks of gestation. Secondary outcomes included miscarriage (pregnancy loss before 24 weeks), stillbirth (fetal death ≥24 weeks), preterm birth (delivery between 24 and 37 weeks), intrauterine growth restriction (estimated fetal weight <10th percentile for gestational age), preeclampsia (according to ACOG criteria), placental abruption, mode of delivery, birth weight, and neonatal outcomes.

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as means with standard deviations for continuous variables and frequencies with percentages for categorical variables. Comparison between groups (successful versus unsuccessful pregnancy outcomes) was performed using Student's t-test for continuous variables and chi-square or Fisher's exact test for categorical variables, as appropriate. Univariate analysis was conducted to identify potential risk factors associated with adverse pregnancy outcomes. Variables with p-values <0.25 in univariate analysis were included in multivariate logistic regression analysis to determine independent predictors of pregnancy outcomes. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated. Survival analysis using Kaplan-Meier curves was performed to estimate cumulative live birth rates over time. A p-value <0.05 was considered statistically significant for all analyses. Sample size calculation was based on previous studies, which indicated that approximately 60-70% of women with RPL achieve successful pregnancy outcomes following appropriate management. With α=0.05 and a power of 80%, a sample size of 100 patients was determined to be sufficient to detect clinically significant associations between risk factors and pregnancy outcomes.

RESULTS

Demographic and Clinical Characteristics

A total of 100 women with recurrent pregnancy loss (RPL) were enrolled in the study. The mean age of participants was 29.4 ± 4.7 years (range: 20-39 years). The majority (65%) of patients were between 25 and 34 years of age. The mean body mass index (BMI) was 26.3 ± 4.2 kg/m² with 42% of participants being overweight (BMI 25-29.9 kg/m²) and 18% obese (BMI ≥30 kg/m²). The median number of previous pregnancy losses was 3 (range: 2-7), with 58% having experienced 2-3 losses and 42% having 4 or more losses. Table 1 summarizes the demographic and baseline clinical characteristics of the study population.

Table 1: Demographic and Baseline Clinical Characteristics of Women with Recurrent Pregnancy Loss (N=100)

Characteristic	Number (%) or Mean ± SD

Age (years)	
<25	21 (21%)
25-29	34 (34%)
30-34	31 (31%)
≥35	14 (14%)
Mean age	29.4 ± 4.7
BMI (kg/m²)	
<18.5 (Underweight)	5 (5%)
18.5-24.9 (Normal)	35 (35%)
25-29.9 (Overweight)	42 (42%)
≥30 (Obese)	18 (18%)
Mean BMI	26.3 ± 4.2
Previous pregnancy losses	
2	32 (32%)
3	26 (26%)
4	22 (22%)
≥5	20 (20%)
Median (range)	3 (2-7)
Educational status	
Primary	12 (12%)
Secondary	28 (28%)
Higher secondary	31 (31%)
Graduate and above	29 (29%)
Socioeconomic status	
Low	26 (26%)
Middle	54 (54%)
High	20 (20%)
Residence	
Urban	64 (64%)
Rural	36 (36%)
Consanguinity	14 (14%)
Family history of RPL	18 (18%)

Etiological Factors

Identifiable causes of RPL were found in 73 patients (73%), while 27 patients (27%) had unexplained RPL. The most common etiological factors were endocrine disorders (42%), anatomical factors (24%), and antiphospholipid syndrome (18%). Among endocrine factors, polycystic ovary syndrome (PCOS) was the most prevalent (24%), followed by hypothyroidism (12%) and luteal phase defect (6%). Uterine septum was the predominant anatomical abnormality (14%), while other anomalies included intrauterine adhesions (5%), submucous fibroids (3%), and bicornuate uterus (2%). Table 2 presents the distribution of etiological factors among the study population.

Table 2: Distribution of Etiological Factors in Women with Recurrent Pregnancy Loss (N=100)

Etiological Factor	**Number (%)**
Endocrine factors	**42 (42%)**
Polycystic ovary syndrome	24 (24%)
Hypothyroidism	12 (12%)
Luteal phase defect	6 (6%)
Anatomical factors	**24 (24%)**
Uterine septum	14 (14%)

Intrauterine adhesions	5 (5%)
Submucous fibroids	3 (3%)
Bicornuate uterus	2 (2%)
Immunological factors	**18 (18%)**
Antiphospholipid syndrome	18 (18%)
Thrombophilias	**8 (8%)**
Protein S deficiency	6 (6%)
Protein C deficiency	2 (2%)
Chromosomal abnormalities	**6 (6%)**
Balanced translocation	4 (4%)
Other chromosomal anomalies	2 (2%)
Unexplained	**27 (27%)**

Note: Some patients had multiple etiological factors; hence, the total exceeds 100%.

Pregnancy Outcomes

Of the 100 women enrolled, 87 conceived during the study period, with a median time to conception of 4.2 months (range: 1-18 months). Among those who conceived, 61 (70.1%) had live births, while 26 (29.9%) experienced adverse pregnancy outcomes, including 18 (20.7%) miscarriages, 4 (4.6%) stillbirths, and 4 (4.6%) neonatal deaths. The overall successful pregnancy rate (defined as live birth) was 61% for the entire cohort and 70.1% for those who conceived.

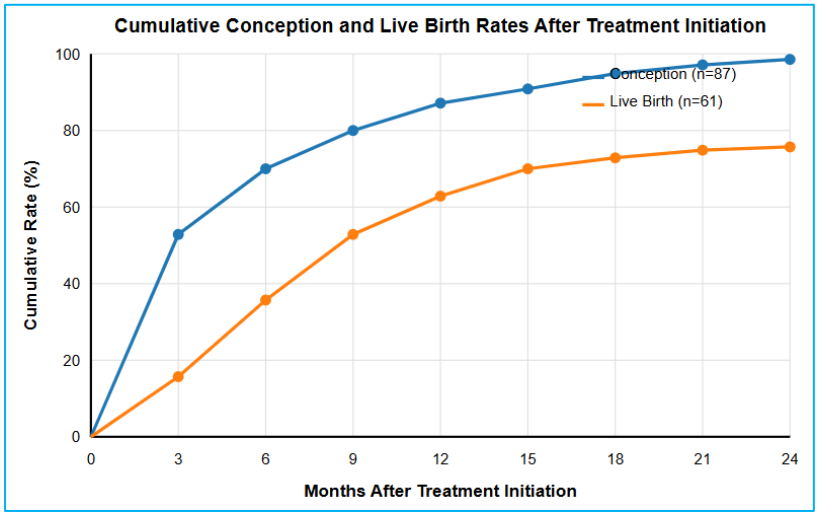

Fig1: Kaplan-Meier curve showing cumulative conception and live birth rates over time (months) following treatment initiation.

Table 3 summarizes the pregnancy outcomes stratified by identified etiological factors. The highest live birth rates were observed in women with anatomical factors (83.3%), followed by endocrine disorders (76.5%) and unexplained RPL (69.6%). Women with immunological factors and thrombophilias had lower success rates (57.1% and 50%, respectively). The lowest success rate was observed in women with chromosomal abnormalities (33.3%).

Table 3: Pregnancy Outcomes According to Etiological Factors

Etiological Factor	Conceived/Total (%)	Live Birth/Conceived (%)	Miscarriage (%)	Stillbirth (%)	Neonatal Death (%)
Endocrine (n=42)	34/42 (81.0%)	26/34 (76.5%)	6/34 (17.6%)	1/34 (2.9%)	1/34 (2.9%)
Anatomical	18/24 (75.0%)	15/18 (83.3%)	2/18 (11.1%)	0/18 (0%)	1/18

(n=24)					(5.6%)
Immunological (n=18)	14/18 (77.8%)	8/14 (57.1%)	4/14 (28.6%)	1/14 (7.1%)	1/14 (7.1%)
Thrombophilias (n=8)	6/8 (75.0%)	3/6 (50.0%)	2/6 (33.3%)	1/6 (16.7%)	0/6 (0%)
Chromosomal (n=6)	3/6 (50.0%)	1/3 (33.3%)	2/3 (66.7%)	0/3 (0%)	0/3 (0%)
Unexplained (n=27)	23/27 (85.2%)	16/23 (69.6%)	5/23 (21.7%)	1/23 (4.3%)	1/23 (4.3%)
Total (N=100)	**87/100 (87.0%)**	**61/87 (70.1%)**	**18/87 (20.7%)**	**4/87 (4.6%)**	**4/87 (4.6%)**

Note: Some patients had multiple etiological factors; they were categorized according to the predominant factor.

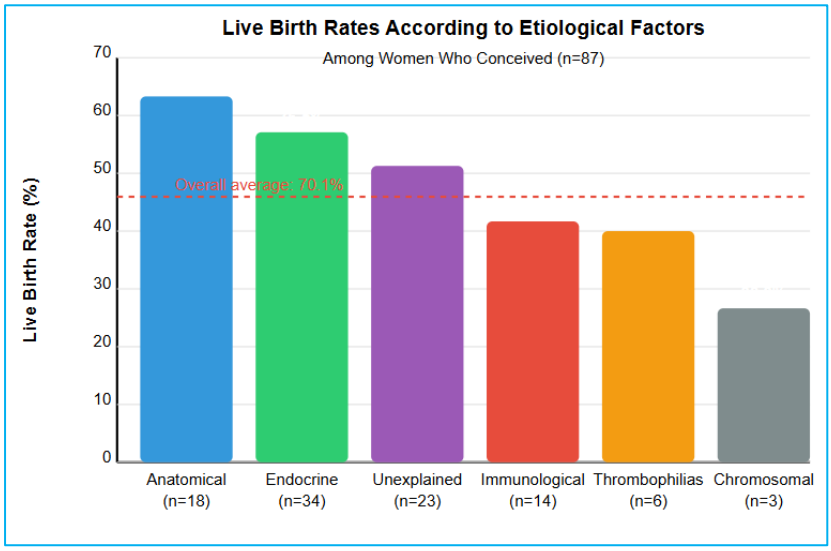

Fig 2: Bar chart comparing live birth rates across different etiological categories.]

Obstetric and Neonatal Outcomes

Among the 61 women who had live births, various obstetric complications were observed. Preterm delivery occurred in 14 (23.0%) cases, with 3 (4.9%) being very preterm (<32 weeks). Preeclampsia was diagnosed in 9 (14.8%) women, and gestational diabetes mellitus in 12 (19.7%). Other complications included intrauterine growth restriction (13.1%), placenta previa (4.9%), and placental abruption (3.3%). Cesarean section was performed in 40 (65.6%) women, with the most common indications being fetal distress (30%), previous cesarean section (25%), and breech presentation (17.5%).The mean birth weight was 2842 ± 618 grams, with 16.4% of neonates being low birth weight (<2500 g). Four neonatal deaths occurred, resulting in a neonatal mortality rate of 6.6% among live births. The causes of neonatal death were extreme prematurity with respiratory distress syndrome (2), congenital anomalies (1), and neonatal sepsis (1). Table 4 presents the obstetric and neonatal outcomes of the successful pregnancies.

Table 4: Obstetric and Neonatal Outcomes in Women with Live Births (n=61)

Outcome	**Number (%) or Mean ± SD**
Gestational age at delivery (weeks)	
<32 (Very preterm)	3 (4.9%)
32-36+6 (Preterm)	11 (18.0%)
≥37 (Term)	47 (77.0%)

Mean gestational age	37.3 ± 2.8
Obstetric complications	
Preeclampsia	9 (14.8%)
Gestational diabetes mellitus	12 (19.7%)
Intrauterine growth restriction	8 (13.1%)
Placenta previa	3 (4.9%)
Placental abruption	2 (3.3%)
Preterm premature rupture of membranes	7 (11.5%)
Mode of delivery	
Vaginal delivery	21 (34.4%)
Cesarean section	40 (65.6%)
Indications for cesarean section (n=40)	
Fetal distress	12 (30.0%)
Previous cesarean section	10 (25.0%)
Breech presentation	7 (17.5%)
Failed induction	5 (12.5%)
Severe preeclampsia	4 (10.0%)
Others	2 (5.0%)
Birth weight (grams)	
<1500 (Very low birth weight)	2 (3.3%)
1500-2499 (Low birth weight)	8 (13.1%)
2500-3999 (Normal birth weight)	49 (80.3%)
≥4000 (Macrosomia)	2 (3.3%)
Mean birth weight	2842 ± 618
Neonatal outcomes	
APGAR score <7 at 5 minutes	5 (8.2%)
NICU admission	9 (14.8%)
Neonatal death	4 (6.6%)

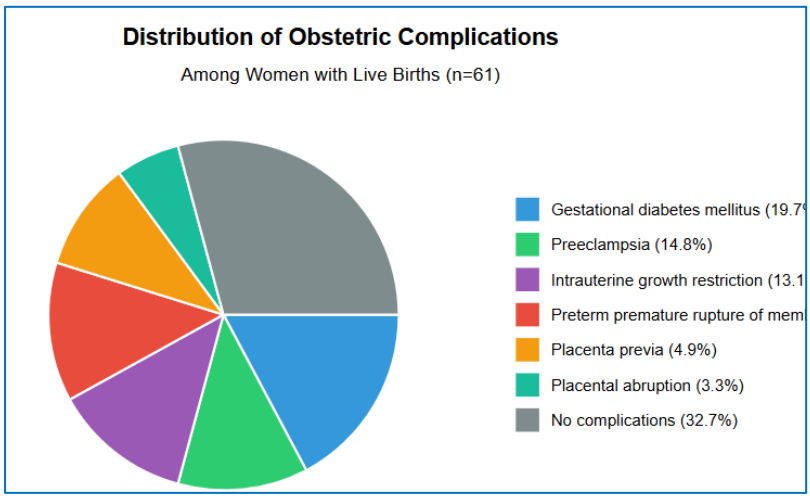

Fig 3: Pie chart showing the distribution of obstetric complications among women with live births.

Risk Factors Associated with Adverse Pregnancy Outcomes

Univariate analysis identified several factors associated with adverse pregnancy outcomes (miscarriage, stillbirth, or neonatal death) among women who conceived. These included advanced maternal age (≥35 years), obesity (BMI ≥30 kg/m²), higher number of previous losses (≥4), presence of antiphospholipid syndrome, thrombophilias, and chromosomal abnormalities. Table 5 presents the univariate analysis of

potential risk factors.

Table 5: Univariate Analysis of Risk Factors for Adverse Pregnancy Outcomes

Risk Factor	Adverse Outcome (n=26)	Successful Outcome (n=61)	Odds Ratio (95% CI)	P-value
Maternal age				
<35 years	18/75 (24.0%)	57/75 (76.0%)	Reference	-
≥35 years	8/12 (66.7%)	4/12 (33.3%)	6.33 (1.74-23.09)	0.003
BMI				
<30 kg/m²	17/73 (23.3%)	56/73 (76.7%)	Reference	-
≥30 kg/m²	9/14 (64.3%)	5/14 (35.7%)	5.93 (1.78-19.76)	0.002
Number of previous losses				
2-3	10/51 (19.6%)	41/51 (80.4%)	Reference	-
≥4	16/36 (44.4%)	20/36 (55.6%)	3.28 (1.28-8.40)	0.012
Antiphospholipid syndrome				
Absent	16/73 (21.9%)	57/73 (78.1%)	Reference	-
Present	10/14 (71.4%)	4/14 (28.6%)	8.91 (2.49-31.88)	<0.001
Thrombophilias				
Absent	23/81 (28.4%)	58/81 (71.6%)	Reference	-
Present	3/6 (50.0%)	3/6 (50.0%)	2.52 (0.48-13.31)	0.355
Chromosomal abnormalities				
Absent	24/84 (28.6%)	60/84 (71.4%)	Reference	-
Present	2/3 (66.7%)	1/3 (33.3%)	5.00 (0.44-57.28)	0.198
PCOS				
Absent	21/63 (33.3%)	42/63 (66.7%)	Reference	-
Present	5/24 (20.8%)	19/24 (79.2%)	0.53 (0.17-1.60)	0.256
Hypothyroidism				
Absent	24/75 (32.0%)	51/75 (68.0%)	Reference	-
Present	2/12 (16.7%)	10/12 (83.3%)	0.43 (0.09-2.10)	0.293
Uterine anomalies				
Absent	23/69 (33.3%)	46/69 (66.7%)	Reference	-
Present	3/18 (16.7%)	15/18 (83.3%)	0.40 (0.11-1.51)	0.168
Treatment modality				
Medical only	22/69 (31.9%)	47/69 (68.1%)	Reference	-
Surgical ± Medical	4/18 (22.2%)	14/18 (77.8%)	0.61 (0.18-2.06)	0.423

Multivariate logistic regression analysis revealed that four factors were independently associated with adverse pregnancy outcomes: maternal age ≥35 years (adjusted OR 4.82, 95% CI 1.17-19.88, p=0.029), obesity (adjusted OR 4.37, 95% CI 1.18-16.21, p=0.027), ≥4 previous pregnancy losses (adjusted OR 2.95, 95% CI 1.06-8.21, p=0.038), and antiphospholipid syndrome (adjusted OR 7.14, 95% CI 1.82-28.03, p=0.005). Table 6 presents the results of the multivariate analysis.

Table 6: Multivariate Logistic Regression Analysis of Risk Factors for Adverse Pregnancy Outcomes

Risk Factor	Adjusted Odds Ratio	95% Confidence Interval	P-value
Maternal age ≥35 years	4.82	1.17-19.88	0.029
BMI ≥30 kg/m²	4.37	1.18-16.21	0.027
≥4 previous pregnancy losses	2.95	1.06-8.21	0.038

Antiphospholipid syndrome	7.14	1.82-28.03	0.005
Chromosomal abnormalities	3.76	0.28-49.85	0.316
Uterine anomalies	0.52	0.13-2.14	0.368

Treatment Modalities and Their Effects

Various treatment modalities were employed based on identified etiological factors. Progesterone supplementation was the most common intervention (72%), followed by low-dose aspirin (42%), low-molecular-weight heparin (26%), and levothyroxine (12%). Surgical interventions were performed in 18% of cases, primarily hysteroscopic metroplasty for uterine septum (14%). Table 7 presents the distribution of treatment modalities and their associated pregnancy outcomes.

Table 7: Treatment Modalities and Associated Pregnancy Outcomes

Treatment Modality	Number of Patients (%)	Conception Rate (%)	Live Birth Rate (%)
Medical treatments			
Progesterone	72 (72%)	64/72 (88.9%)	45/64 (70.3%)
Low-dose aspirin	42 (42%)	36/42 (85.7%)	23/36 (63.9%)
LMWH	26 (26%)	20/26 (76.9%)	11/20 (55.0%)
Levothyroxine	12 (12%)	10/12 (83.3%)	8/10 (80.0%)
Metformin	24 (24%)	20/24 (83.3%)	15/20 (75.0%)
Surgical treatments			
Hysteroscopic metroplasty	14 (14%)	11/14 (78.6%)	9/11 (81.8%)
Hysteroscopic adhesiolysis	5 (5%)	4/5 (80.0%)	3/4 (75.0%)
Myomectomy	3 (3%)	2/3 (66.7%)	2/2 (100%)
Combined approach			
Medical + Surgical	18 (18%)	14/18 (77.8%)	11/14 (78.6%)
Multiple medical therapies	58 (58%)	49/58 (84.5%)	31/49 (63.3%)

Note: Most patients received multiple treatments; percentages are calculated based on the number of patients who received each specific treatment.

The time to conception varied significantly based on the treatment approach. Patients who underwent surgical correction of anatomical factors had a median time to conception of 3.2 months, compared to 4.7 months for those receiving medical treatment only (p=0.028). The median time to conception was significantly longer in women with antiphospholipid syndrome (6.8 months) compared to those without this condition (3.9 months, p=0.003). Among women who conceived, the interval between treatment initiation and conception was inversely associated with successful pregnancy outcome. Women who conceived within 6 months of treatment initiation had a significantly higher live birth rate compared to those who conceived after 6 months (76.9% vs. 54.5%, p=0.041).

DISCUSSION

This prospective observational study investigated the risk factors associated with pregnancy outcomes in 100 women with recurrent pregnancy loss (RPL) who received treatment at the Fetomaternal Medicine Department of BSMMU, Dhaka, Bangladesh. Our findings provide valuable insights into the etiological spectrum, treatment efficacy, and prognostic factors influencing subsequent pregnancy outcomes in a South Asian population.

Etiological Spectrum of RPL

In our cohort, identifiable causes of RPL were found in 73% of patients, with endocrine disorders (42%), anatomical factors (24%), and immunological factors (18%) being the most prevalent. This distribution

is somewhat different from that reported in Western populations, where unexplained RPL typically accounts for 50-75% of cases. [18,19] The higher proportion of identifiable causes in our study may be attributed to several factors, including differences in genetic background, environmental exposures, and the comprehensive evaluation protocol employed at our institution.The predominance of endocrine disorders, particularly PCOS (24%) and hypothyroidism (12%), aligns with previous studies from South Asian populations. Rai et al. [20] reported PCOS in 29.3% of Indian women with RPL, while Bahadur et al. [21] found thyroid dysfunction in 14.8% of such patients. The high prevalence of PCOS in our cohort may reflect the increasing trend of metabolic disorders in Bangladesh, influenced by changing lifestyle patterns and nutritional transitions. [22] Similarly, the substantial proportion of hypothyroidism may be related to iodine deficiency that persists in certain regions of Bangladesh despite national iodization programs. [23] Anatomical factors, particularly uterine septum (14%), were the second most common etiological category in our study. This is comparable to findings from other developing countries; Saraveloset al. [24] in a meta-analysis reported uterine anomalies in 15.4% of women with RPL. The relatively high prevalence of intrauterine adhesions (5%) in our cohort may reflect the impact of postpartum and post-abortion infections, which remain significant concerns in resource-limited settings with suboptimal access to sterile procedures and antibiotics. [25] Antiphospholipid syndrome (APS) was identified in 18% of our patients, which is consistent with the global prevalence range of 5-20% reported in RPL populations. [26] However, the true prevalence of thrombophilias (8%) may be underestimated in our cohort due to the selective screening approach necessitated by resource constraints. Western studies employing comprehensive thrombophilia screening have reported prevalence rates of 15-30% in RPL patients. [27] This highlights the need for context-specific evaluation protocols that balance diagnostic thoroughness with resource availability.The prevalence of chromosomal abnormalities (6%) in our study is lower than the 2-5% reported in partners of couples with RPL by De Braekeleeret al. [28] This discrepancy may be partly explained by our selective approach to karyotyping, which was performed only in couples with three or more losses or a family history of genetic disorders. Additionally, advanced cytogenetic techniques such as array comparative genomic hybridization were not routinely available at our institution during the study period, potentially limiting the detection of submicroscopic chromosomal imbalances. [29]

Pregnancy Outcomes and Their Determinants

Our study demonstrated an overall live birth rate of 61% for the entire cohort and 70.1% among those who conceived, which is comparable to the success rates reported in international literature. Brigham et al. [30] reported a live birth rate of 71% in their cohort of RPL patients, while the PROMISE trial [31] observed a 65.8% live birth rate in women with unexplained RPL. The slightly higher success rate in our unexplained RPL group (69.6%) compared to some Western studies might reflect differences in patient characteristics, treatment approaches, or the intense surveillance provided at our specialized center.The stratification of pregnancy outcomes by etiological factors revealed significant variations in success rates. Women with anatomical factors had the highest live birth rate (83.3%), which aligns with findings by Valle and Ekpo[32], who reported success rates of 80-90% following hysteroscopic correction of uterine abnormalities. Similarly, the relatively high success rate in endocrine disorders (76.5%) is consistent with findings by Li et al. [33], who reported a 74.2% live birth rate following treatment of thyroid dysfunction in RPL patients. Conversely, the poor outcomes in women with chromosomal abnormalities (33.3% live birth rate) corroborate previous observations by Franssen et al. [34], who reported success rates of 25-40% in such cases, reflecting the limited therapeutic options for genetic etiologies.Multivariate analysis identified four independent risk factors for adverse pregnancy outcomes: advanced maternal age (≥35 years), obesity (BMI ≥30 kg/m²), higher number of previous losses (≥4), and antiphospholipid syndrome. The adverse impact of maternal age has been consistently reported in previous studies; Grande et al. [35] found that women over 35 years had a 2.7-fold increased risk of miscarriage compared to younger women, which is lower than our adjusted OR of 4.82. This difference may reflect the greater vulnerability of older women in our setting, where advanced maternal age often coexists with nutritional deficiencies, chronic infections, and limited access to specialized

antenatal care. [36] The significant association between obesity and adverse outcomes (adjusted OR 4.37) is consistent with findings by Lashen et al. [37], who reported a 1.7-fold increased risk of recurrent miscarriage in obese women. The stronger association in our cohort might be explained by the higher prevalence of metabolic syndrome components and insulin resistance in South Asian populations at lower BMI thresholds, a phenomenon termed the "Asian Indian Phenotype."[38] This underscores the importance of pre-conception weight optimization in RPL management, particularly in populations with heightened metabolic vulnerability. The number of previous losses emerged as a significant prognostic factor in our study, with ≥4 losses associated with nearly threefold higher odds of adverse outcomes (adjusted OR 2.95). This aligns with the findings of Lund et al. [39], who reported decreasing success rates with each additional pregnancy loss in their Danish cohort. This relationship might reflect the increasing likelihood of underlying genetic or structural abnormalities with each successive loss, as suggested by Jaslow et al. [40] However, it is encouraging that even in women with ≥4 losses, the live birth rate remained substantial (55.6%), offering hope for couples with multiple losses. Antiphospholipid syndrome demonstrated the strongest association with adverse outcomes in our cohort (adjusted OR 7.14), despite standard treatment with aspirin and heparin. This is considerably higher than the odds ratios reported in Western studies; Empson et al. [41] found a 2.4-fold increased risk of adverse outcomes in treated APS patients. The poorer outcomes in our setting might reflect delayed diagnosis, suboptimal adherence to anticoagulation regimens, or genetic differences in thrombophilic tendencies among Bangladeshi women. [42] These findings highlight APS as a particularly challenging condition in our population, necessitating more intensive monitoring and possibly modified treatment protocols.

Treatment Modalities and Their Efficacy

Our study employed a range of interventions based on identified etiological factors, with progesterone supplementation (72%) and aspirin (42%) being the most commonly used medications. The high utilization of progesterone reflects its empirical use in unexplained RPL and as adjunctive therapy in various other etiologies. While the PROMISE trial questioned the efficacy of progesterone in unexplained RPL, other studies such as PRISM [43] suggested benefits in women with early pregnancy bleeding, and Coomarasamy et al. [44] found potential advantages in women with recurrent pregnancy losses. The pragmatic approach at our institution favors progesterone use given its safety profile and the limited availability of alternative evidence-based interventions for unexplained RPL.Surgical interventions, particularly hysteroscopic metroplasty for uterine septum, demonstrated excellent outcomes in our cohort, with an 81.8% live birth rate. This success rate is comparable to that reported by Venetis et al. [45] in their systematic review (76.3%). The shorter time to conception following surgical correction (median 3.2 months vs. 4.7 months for medical treatment alone) further supports the efficacy of this approach. However, it is important to note that randomized controlled trials evaluating the benefits of septum resection are lacking, and recent guidelines from the European Society of Human Reproduction and Embryology (ESHRE)[46] suggest that high-quality evidence for this intervention remains limited.The interval between treatment initiation and conception emerged as an important prognostic factor in our study, with significantly higher live birth rates in women who conceived within 6 months of treatment (76.9% vs. 54.5% after 6 months). This temporal relationship has been previously reported by Kaandorpet al. [47], who found decreasing success rates with increasing time to conception in women with unexplained RPL. This observation might reflect the waning efficacy of interventions over time or the selection of more refractory cases among later conceivers. From a clinical perspective, this finding supports the importance of optimized pre-conception care and timely conception attempts following treatment initiation.

Obstetric and Neonatal Outcomes

Our study revealed a substantial burden of obstetric complications among women with previous RPL, including preterm delivery (23.0%), gestational diabetes (19.7%), and preeclampsia (14.8%). These rates are higher than those reported in the general Bangladeshi obstetric population [48], suggesting that

women with RPL represent a high-risk group requiring enhanced antenatal surveillance. The elevated risk of adverse outcomes may reflect shared pathophysiological mechanisms between RPL and other pregnancy complications, particularly those involving placental dysfunction. [49] The high cesarean section rate in our cohort (65.6%) exceeds the national average of 33% reported by the Bangladesh Demographic and Health Survey [50], but is comparable to rates observed in other specialized centers managing high-risk pregnancies. This elevated rate likely reflects both medical indications in this vulnerable population and the increasing trend of cesarean deliveries in urban Bangladesh. [51] The primary indications for cesarean section in our cohort (fetal distress, previous cesarean, and breech presentation) mirror those reported in other studies from tertiary centers in Bangladesh. [52] The neonatal outcomes in our study underscore the ongoing challenges in achieving optimal perinatal health in resource-limited settings. The proportion of low-birth-weight infants (16.4%) and the neonatal mortality rate (6.6%) are considerably higher than those observed in RPL cohorts from high-income countries. Fawzy et al. [53] reported a low-birth-weight rate of 9.2% and neonatal mortality of 1.8% in their Egyptian cohort of RPL patients. The less favorable outcomes in our setting highlight the importance of a comprehensive approach that extends beyond achieving pregnancy to ensuring optimal maternal-fetal health throughout gestation and the neonatal period.

Implications for Clinical Practice

Our findings have several important implications for the management of RPL in resource-limited settings. First, the relatively high proportion of identifiable causes in our cohort (73%) underscores the value of a systematic evaluation protocol, even in settings with constrained resources. A targeted approach focusing on the most prevalent etiologies (endocrine, anatomical, and immunological factors) may offer a cost-effective strategy for the initial evaluation of RPL patients in similar contexts. Second, the excellent outcomes following correction of anatomical factors (83.3% live birth rate) and treatment of endocrine disorders (76.5%) highlight the importance of identifying and addressing these conditions. The implementation of basic diagnostic modalities such as transvaginal ultrasonography and thyroid function tests should be prioritized in RPL evaluation protocols, given their high yield and therapeutic implications. Third, the identification of specific risk factors for adverse outcomes (advanced maternal age, obesity, multiple previous losses, and antiphospholipid syndrome) enables risk stratification and individualized counseling for RPL patients. Women with these high-risk features may benefit from more intensive antenatal surveillance and specialized care, while those without these factors can be reassured about their relatively favorable prognosis. Fourth, the significant obstetric and neonatal complications observed in our cohort emphasize the need for continued vigilance throughout pregnancy in women with RPL history. The implementation of dedicated follow-up protocols focusing on early detection of placental dysfunction, gestational diabetes, and preterm labor may help mitigate these risks and improve overall outcomes. Finally, the shorter interval to conception and higher success rates observed in earlier conceivers support the practice of encouraging timely pregnancy attempts following diagnosis and initial treatment. While this approach must be balanced against the need for adequate preparation and optimization, prolonged delays in conception attempts may be associated with diminished success rates in some patients.

Strengths and Limitations

The strengths of our study include its prospective design, comprehensive evaluation protocol, standardized treatment approach, and complete follow-up of pregnancy outcomes. The diverse socioeconomic and educational background of our participants enhances the generalizability of our findings to the broader Bangladeshi population. Additionally, our study provides valuable data on RPL from a South Asian perspective, addressing a significant knowledge gap in the existing literature. However, several limitations should be acknowledged. First, the single-center design and specialized tertiary care setting may limit the applicability of our findings to primary care contexts. Second, the selective approach to certain investigations (thrombophilia screening, karyotyping) due to resource constraints may have resulted in underestimation of these etiologies. Third, the sample size, while

adequate for the primary analyses, limited the power for subgroup analyses and evaluation of rare risk factors. Fourth, the observational design precludes definitive conclusions regarding treatment efficacy, which would require randomized controlled trials. Finally, the relatively short follow-up period may have underestimated the cumulative live birth rate, particularly in women who required multiple conception attempts.

Future Directions

Our findings highlight several areas for future research. Large-scale, multicenter studies encompassing diverse healthcare settings in Bangladesh would enhance the generalizability of results and enable the development of context-specific guidelines. Long-term follow-up studies exploring the recurrence risk of complications and outcomes of subsequent pregnancies would provide valuable information for counseling women with RPL. Randomized controlled trials evaluating the efficacy of interventions in specific subgroups, particularly those with unexplained RPL or antiphospholipid syndrome, would address critical knowledge gaps in these challenging areas. Finally, implementation research focused on developing cost-effective evaluation and treatment protocols for resource-limited settings would translate research findings into practical improvements in care delivery.

CONCLUSION

This prospective study of 100 women with recurrent pregnancy loss treated at BSMMU in Bangladesh provides valuable insights into the etiological spectrum, treatment outcomes, and prognostic factors in a South Asian population. Our findings demonstrate that a systematic evaluation can identify causative factors in a majority of cases (73%), with endocrine disorders, anatomical factors, and immunological conditions constituting the most prevalent etiologies. The overall successful pregnancy rate of 70.1% among those who conceived offers encouraging evidence that appropriate management can lead to favorable outcomes for most women with RPL. Four independent risk factors were identified for adverse pregnancy outcomes: advanced maternal age (≥35 years), obesity (BMI ≥30 kg/m²), higher number of previous losses (≥4), and antiphospholipid syndrome. These factors can guide risk stratification and personalized counseling, allowing clinicians to identify high-risk patients who require more intensive surveillance and support. Our findings contribute to the limited body of evidence regarding RPL in resource-constrained settings and suggest that implementation of a structured evaluation and treatment protocol adapted to local resources can yield outcomes comparable to those reported in high-income countries. However, challenges remain, particularly in the management of antiphospholipid syndrome and chromosomal abnormalities, where success rates remain suboptimal. In conclusion, our study demonstrates that with systematic evaluation and targeted management, favorable pregnancy outcomes can be achieved in a majority of women with RPL, offering hope to couples experiencing this distressing condition. The identification of specific risk factors for adverse outcomes enables individualized prognostication and focused surveillance, representing an important step toward precision medicine in the field of reproductive health.

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