Comparison of Fibrinogen/Albumin Ratio Between Women With Recurrent Pregnancy Loss and Those With First-Time Miscarriage

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Abstract- The fibrinogen/albumin ratio (FAR) serves as a valuable marker of systemic inflammation and coagulation. However, its capacity to distinguish patients with recurrent pregnancy loss (RPL) from those experiencing a first-time spontaneous miscarriage has yet to be established. This study aimed to compare FAR levels between women with RPL and those who underwent a first-trimester miscarriage, as well as to assess the discriminative performance of FAR using receiver operating characteristic (ROC) curve analysis. In this cross-sectional, diagnostic-comparison study, 120 women in their first trimester were enrolled and divided into three groups: RPL, first-time miscarriage, and healthy early pregnancy (n=40 per group). Plasma fibrinogen and serum albumin levels were measured, and the FAR was calculated. Differences between the groups were analyzed using appropriate parametric or nonparametric methods. Subsequently, ROC analysis was performed to evaluate the area under the curve (AUC), optimal cut-off points (via the Youden index), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Women with RPL, compared with healthy pregnant controls, were characterized by significantly elevated fibrinogen (403.50±15.62 mg/dL vs 307.25±45.35 mg/dL), decreased albumin (332.25±32.78 mg/dL vs 376.25±44.36 mg/dL), and markedly increased FAR levels (1.2425±0.0699 vs 0.8289±0.1566) (all P<0.001). Compared with the first-time miscarriage group, the RPL group also showed higher fibrinogen (403.50±15.62 mg/dL vs 354.75±28.99 mg/dL), lower albumin (332.25±32.78 mg/dL vs 345.50±39.68 mg/dL), and higher FAR (1.2425±0.0699 vs 1.0434±0.1023) (P≤0.002). ROC analysis identified an FAR cut-off value of 0.975 for discriminating between RPL and healthy pregnancy (AUC=0.875; sensitivity 82.5%; specificity 87.5%) and 1.083 for discriminating between RPL and first-time miscarriage (AUC=0.777; sensitivity 57.5%; specificity 65.0%). FAR is significantly elevated in women with RPL and strongly discriminates between RPL and healthy early pregnancy. It moderately discriminates between RPL and first-time miscarriage, suggesting that it could be useful as a screening/stratification biomarker but should not be used as a single diagnostic test for distinguishing between miscarriage subtypes. External multicenter validation, harmonized assay methods, and incorporation of FAR into multimarker predictive models are recommended prior to clinical implementation.

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Introduction

Recurrent pregnancy loss (RPL), defined usually as two consecutive clinical pregnancy losses, is a distressing reproductive disorder with severe psychological and clinical ramifications, having a reported incidence of approximately 1-5% in couples trying for pregnancy, the exact number varying according to population and

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definition (1-3).

Dysregulated inflammation and haemostatic imbalance are increasingly recognized as underlying mechanisms of early pregnancy loss. Successful implantation and placentation require precisely controlled immune and coagulation processes; conversely, excessive inflammation, untimely inflammatory events, or maternal hypercoagulability at the maternal-fetal interface can inhibit trophoblast invasion, reduce uteroplacental perfusion, and increase the risk of miscarriage (4-6). Acute-phase proteins, such as fibrinogen and albumin, exhibit opposing responses: fibrinogen is a positive acute-phase reactant essential for fibrin formation and typically increases during inflammation and pregnancy, whereas albumin is a negative acute-phase protein that decreases in response to systemic inflammation and alterations in nutritional or vascular status. Hemodynamic and hemostatic adaptations to pregnancy, including increased fibrinogen levels and plasma volume changes, must be considered when interpreting variations in single analytes during early gestation (7-8).

By its nature, the interplay between fibrinogen- and albumin-related processes reflects acute-phase responses in opposite directions, making FAR a simple parameter that integrates both hemostatic and inflammatory information. FAR has attracted considerable interest across medical specialties as an inexpensive and readily accessible biomarker of these contrasting acute-phase changes. Observational and biomarker studies in obstetrics have investigated FAR and other coagulation parameters, with several cohorts linking abnormal first-trimester hemostatic profiles to early pregnancy failure (9-11). Although systematic reviews and meta-analyses in other medical fields, such as severe infections and cardiovascular disease, have associated elevated FAR with worse clinical outcomes, studies on its obstetric applications remain limited and have reported heterogeneous findings. In particular, cut-off points, diagnostic performance measures (AUROC, sensitivity, and specificity), and assay platforms have varied across studies; moreover, direct comparative data evaluating FAR as a discriminator between recurrent pregnancy loss and first-time spontaneous miscarriage are scarce. These gaps limit immediate clinical application and highlight the need for rigorous comparative studies and external validation (12-14). Therefore, it is reasonable to investigate whether FAR is higher in women with RPL than in those presenting with a first-time miscarriage and whether FAR demonstrates clinically useful discriminatory performance. Well-designed studies should prespecify ROC analysis with transparent AUC reporting and threshold selection, account for pregnancy-related physiological shifts in analytes, and move toward integrated multimarker models that combine inflammatory, coagulation, and clinical variables to improve risk stratification (15).

Materials and Methods

Study design and setting

This observational, cross-sectional diagnostic-comparison study was conducted at a tertiary obstetrics and gynecology center. The study compared the plasma fibrinogen/serum albumin ratio (FAR) between two groups of women presenting in the first trimester: those with recurrent pregnancy loss (RPL) and those presenting with a first-time spontaneous miscarriage.

Participants

Eligible participants were women presenting to the early pregnancy clinic between 6+0 and 12+6 weeks of gestation with a nonviable intrauterine pregnancy confirmed by ultrasound. Participants were allocated to one of two study groups according to pregnancy history:

RPL group

Women with a documented history of two or more consecutive spontaneous pregnancy losses prior to the index pregnancy.

First-time miscarriage group

Women experiencing their first clinically confirmed spontaneous miscarriage (no prior history of miscarriage).

Inclusion criteria

- Age 18-45 years.
- Gestational age between 6+0 and 12+6 weeks at the time of blood sampling.
- Provision of written informed consent.

Exclusion criteria

- Multiple gestation pregnancy.
- Known major fetal or embryonic chromosomal abnormality in the index pregnancy.
- Current or recent (within 14 days) systemic infection.
- Chronic liver disease, nephrotic syndrome, or other conditions known to markedly alter fibrinogen or albumin independently of pregnancy.

- Use of corticosteroids, systemic anticoagulants, or immunosuppressive therapy within 14 days prior to sampling.
- Elective termination of pregnancy or induced abortion.
- Refusal or inability to provide informed consent.

Sample size

A pragmatic sample size of 40 participants per group (total n=80) was chosen to provide adequate precision for group comparisons and ROC estimation in this diagnostic performance study. This sample size balances feasibility with statistical power to detect moderate differences in FAR, allowing the estimation of the AUC with reasonably narrow confidence intervals for an exploratory diagnostic study. The protocol specifies reporting confidence intervals (CIs) for effect sizes and ROC statistics rather than relying solely on *P*.

Clinical data collection

At enrollment, a standardized case report form was used to record maternal age, gravidity and parity, body mass index (BMI, calculated from measured weight and height), smoking status, relevant comorbidities (including known thrombophilias or autoimmune diseases), medications, and gestational age based on both the last menstrual period and ultrasound. Ultrasound reports confirming nonviable pregnancy were stored in the study database.

Specimen collection and handling

Blood samples were collected by trained phlebotomists in accordance with standard phlebotomy procedures. Participants were asked to fast overnight whenever possible; if fasting was not feasible, fasting status was recorded.

- or fibrinogen measurement, blood was collected into 3.2% sodium citrate tubes (9:1 blood-to-citrate ratio). The tubes were gently inverted, transported at room temperature, and processed within 2 hours. Platelet-poor plasma was prepared by centrifugation at approximately 2,000 g for 15 minutes and was either analyzed immediately or aliquoted and stored at −80° C for batched analysis.
- For albumin measurement, serum separator tubes were used. Blood was allowed to clot for 30 minutes at room temperature, then centrifuged at approximately 1,500-2,000 g for 10 minutes. The serum was then either analyzed immediately or aliquoted and stored at −80° C.

Preanalytical quality control measures included avoidance of hemolysis, documentation of sample collection and processing times, and maintenance of the cold chain where required. All samples were labeled with anonymized study IDs, and laboratory staff were blinded to participant group allocation.

Laboratory assays

Laboratory testing was performed in an accredited clinical laboratory using routine validated methods:

- **Fibrinogen:** Functional fibrinogen was measured using a clot-based method based on the Clauss principle on an automated coagulation analyzer. Results were reported in g/L. Laboratory quality control procedures and calibrations were performed in accordance with the manufacturer's instructions and the laboratory's standard operating procedures.
- **Albumin:** Serum albumin was measured using a routine colorimetric method (bromocresol green or an equivalent assay) on an automated chemistry analyzer. Results were reported in g/L, with daily internal quality control and participation in external quality assurance schemes.

Analytical performance characteristics, including intra- and inter-assay coefficients of variation, limits of detection, and linearity, were recorded. For assays performed in batches, case and control samples were balanced across batches to prevent systematic assay bias.

Calculation of FAR

The fibrinogen/albumin ratio (FAR) was calculated for each participant as follows:

FAR = fibrinogen (g/L) / albumin (g/L)

FAR is a unitless ratio. Raw fibrinogen and albumin values, as well as FAR, were used for descriptive analysis and hypothesis testing. Where appropriate, FAR was also dichotomized using empirically derived thresholds (see Statistical Analysis).

Data quality and management

Study data were entered into a secure electronic database with built-in range checks and audit trails. Data entry was verified by a second researcher for a random 10% sample, and any discrepancies were resolved through source-document verification. Identifiers were

kept separate from the analytical dataset to maintain participant confidentiality.

Statistical analysis

All analyses were prespecified in a statistical analysis plan and carried out using standard statistical software.

- **Descriptive statistics:** Continuous variables were summarized as mean±standard deviation for approximately normally distributed measures, or as median and interquartile range for skewed measures. Categorical variables were summarized as counts and percentages.

Group comparisons

Distributions of fibrinogen, albumin, and FAR were visually inspected using histograms and Q-Q plots. Normality was assessed, and if the data were approximately normally distributed, independent-samples t-tests were used to compare means between groups; if the data were non-normal, Wilcoxon rank-sum tests (Mann-Whitney U tests) were applied. Categorical variables were compared using chi-square tests or Fisher's exact test, as appropriate.

Diagnostic discrimination (ROC analysis)

Receiver-operating characteristic (ROC) analysis was used to quantify the ability of FAR to discriminate between RPL and first-time miscarriage. The area under the ROC curve (AUC) was estimated with 95% confidence intervals. The optimal FAR cut-off point was determined by maximizing the Youden index (sensitivity+specificity-1). Sensitivity, specificity, positive predictive value, and negative predictive value at that cut-off point were reported with 95% confidence intervals. When appropriate, bootstrapping (1,000 resamples) was used to obtain robust confidence intervals.

Multivariable modelling

Logistic regression models were used to assess the association between FAR and RPL status, adjusting for prespecified covariates, including maternal age, BMI, gestational age at sampling, and smoking status. FAR was modeled both as a continuous predictor (per 0.1-unit increase) and as a categorical variable using the ROC-derived threshold. Model discrimination and calibration were evaluated, and adjusted odds ratios with 95% confidence intervals were reported.

Additional analyses

Comparisons of AUCs for FAR versus the individual biomarkers, fibrinogen and albumin, were performed using standard nonparametric methods for correlated ROC curves. Sensitivity analyses included repeating the main analyses after excluding outliers, stratifying by gestational age window (6-8 weeks vs 9-12 weeks), and assessing the impact of fasting status.

All hypothesis tests were two-sided, and a significance threshold of $P<0.05$ was applied. Exact P values and confidence intervals were reported.

Blinding and bias minimization

Laboratory personnel were blinded to clinical group assignment. Case selection and enrollment followed prespecified criteria to reduce selection bias. Data analysts were also blinded to group identity during the primary analyses through the use of coded group labels until the main outcomes were finalized.

The study protocol was approved by the institutional ethics committee. All participants provided written informed consent. The results will be disseminated through peer-reviewed publications and presentations. Anonymized data and statistical code will be made available upon reasonable request and subject to governance approvals.

Results

Study population

One hundred and twenty (120) women in their first trimester were included in the study. Participants were divided into three equal groups (n=40 each) for analysis: recurrent pregnancy loss (RPL; group A1), first-time miscarriage (group A2), and healthy early pregnancy controls (group B). Baseline demographics and obstetric characteristics of the study participants are presented in Table 1**.**

The data indicate that women in the RPL group were older and had higher gravidity and parity than those in the two comparison groups (all $P\leq0.008$). Employment status and certain sociodemographic distributions also differed across groups, while differences in education level did not reach statistical significance in this sample.

Women with RPL had significantly higher fibrinogen levels, lower albumin levels, and markedly higher FAR than healthy pregnant controls as shown in Table 2 (all comparisons $P=0.0001$), indicating a combined inflammatory and coagulative shift in the RPL group. These differences underpin the strong discriminatory performance of FAR versus healthy pregnancy observed in the ROC analysis.

Compared with women experiencing a first-time miscarriage, the RPL group showed significantly higher

fibrinogen and FAR levels and lower albumin levels (fibrinogen and FAR, *P*=0.0001; albumin, *P*=0.002) as shown in Table 3. These subgroup differences support evaluating the discriminative ability of FAR between RPL and first-time miscarriage.

At the empirical cut-off point of 0.975, FAR demonstrated excellent discrimination between RPL and healthy early pregnancy as shown in Table 4 (AUC=0.875, 95% CI 0.800-0.950), with high sensitivity and specificity. This supports the potential utility of FAR in identifying women with RPL when compared to those with uncomplicated pregnancies.

In contrast, FAR discriminated RPL from first-time miscarriage only moderately (AUC=0.777) at the identified cut-off point (1.083), with modest sensitivity and specificity (Table 5). This indicates that FAR alone has limited power to reliably distinguish recurrent from single-event miscarriage in this cohort.

Table 1. Sociodemographic and obstetric features of study groups (n=120)

VARIABLE	RPL (A1) (n=40)	First-time miscarriage (A2) (n=40)	Healthy pregnancy (B) (n=40)	*P*
AGE (YEARS), MEAN ± SD	29.78 ± 5.41	24.75 ± 4.60	23.15 ± 3.67	0.0001
GRAVIDITY, MEAN ± SD	5.00 ± 1.73	2.78 ± 0.77	3.55 ± 1.13	0.0001
PARITY, MEAN ± SD	2.35 ± 1.42	1.78 ± 0.77	2.55 ± 1.13	0.008
OCCUPATION — HOUSEWIFE, N	35	40	32	0.015
OCCUPATION — EMPLOYED, N	5	0	8	0.015
EDUCATION — ILLITERATE, N	0	8	3	0.067
EDUCATION — PRIMARY, N	12	9	10	0.067
EDUCATION — SECONDARY, N	16	17	19	0.067

Table 2. Plasma fibrinogen, serum albumin and fibrinogen/albumin ratio — RPL (A1) vs Healthy pregnancy (B)

Laboratory variable (units)	RPL (A1) mean ± SD	Healthy pregnancy (B) mean ± SD	*P*
Plasma fibrinogen (mg/dL)	403.50 ± 15.616	307.25 ± 45.347	0.0001
Serum albumin (mg/dL)	332.25 ± 32.776	376.25 ± 44.358	0.0001
Fibrinogen/Albumin Ratio (FAR, unitless)	1.2425 ± 0.06995	0.8289 ± 0.15664	0.0001

Table 3. Plasma fibrinogen, serum albumin and FAR — RPL (A1) vs First-time miscarriage (A2)

Laboratory variable (units)	RPL (A1) mean ± SD	First-time miscarriage (A2) mean ± SD	*P*
Plasma fibrinogen (mg/dL)	403.50 ± 15.616	354.75 ± 28.999	0.0001
Serum albumin (mg/dL)	332.25 ± 32.776	345.50 ± 39.675	0.002
Fibrinogen/Albumin Ratio (FAR)	1.2425 ± 0.06995	1.0434 ± 0.10234	0.0001

Table 4. ROC analysis — Fibrinogen/Albumin Ratio (RPL vs Healthy pregnancy)

Statistic	Value
Cut-off point (CP)	0.975
AUC (area under ROC)	0.875
Standard error (AUC)	0.038
95% CI for AUC	0.800 – 0.950
Sensitivity (SN)	82.5%
Specificity (SP)	87.5%
Positive predictive value (PPV)	86.8%
Negative predictive value (NPV)	83.3%
Accuracy (ACC)	85.0%
***P* (AUC vs 0.5)**	0.000

Table 5. ROC analysis — Fibrinogen/Albumin Ratio (RPL vs First-time miscarriage)

Statistic	Value
Cut-off point (CP)	1.083
AUC (area under ROC)	0.777
Sensitivity (SN)	57.5%
Specificity (SP)	65.0%
Positive predictive value (PPV)	62.2%
Negative predictive value (NPV)	60.5%
Accuracy (ACC)	61.25%

Key findings

All group comparisons reported above were performed using the same methods described in the Methods section (parametric or nonparametric, as appropriate), and the *P* are those reported in the study. The overall pattern of findings—higher fibrinogen, lower albumin, and higher FAR in RPL compared with healthy pregnancy, together with elevated but less discriminatory FAR compared with first-time miscarriage—was consistent across the reported analyses and supports the study's main conclusions regarding FAR as a marker of inflammatory and procoagulant tendency in RPL.

Discussion

In this first-trimester case-control study, women with recurrent pregnancy loss (RPL) exhibited higher plasma fibrinogen levels and lower serum albumin levels, resulting in a significantly higher fibrinogen-to-albumin ratio (FAR) compared to both healthy early pregnancy controls and women presenting with a first-time spontaneous miscarriage. FAR yielded excellent discrimination from healthy pregnancy but only moderate discrimination from first-time miscarriage (16). These findings align with data from a single-center clinical study that recently proposed FAR as a potential biomarker for evaluating early pregnancy complications; that cohort demonstrated increased FAR in women with recurrent losses and suggested a predictive role for FAR in RPL assessment (11). Research on threatened miscarriage cohorts has likewise demonstrated higher FAR levels, with poorer short-term outcomes recorded in cases where FAR was elevated. This supports the interpretation of FAR as an early pregnancy risk indicator influenced by the interplay between inflammation and hemostasis, rather than a single etiology (10). Furthermore, broader studies of first-trimester hemostatic parameters have described changes in coagulation markers—including fibrinogen, aPTT, and thrombin time—in pregnancies that subsequently failed. This suggests that hemostatic activation may be measurable, potentially accompanying or even preceding implantation failure and the disruption of early placentation (9).

The finding of increased fibrinogen levels in RPL is consistent with obstetric literature linking elevated fibrinogen, along with other markers of procoagulant activity, to adverse outcomes in early pregnancy. Parallel work in preeclampsia cohorts has shown that FAR increases with disease severity, suggesting that alterations in acute-phase reactants and coagulation indices characterize the severity of placental disorders more broadly and are not unique to miscarriage phenotypes (14). Systematic reviews of FAR in non-obstetric settings, including severe infection and oncology, have also demonstrated robust associations between higher FAR values and worse clinical outcomes, further supporting the biological plausibility of FAR as a marker of generalized inflammatory-hemostatic stress relevant to pregnancy pathophysiology (17-18). At the molecular level, comparative proteomic and multi-omics studies have identified altered decidual and placental pathways in RPL, including oxidative phosphorylation/mitochondrial dysfunction and dysregulated RNA processing, which may ultimately contribute to systemic changes in acute-phase proteins and coagulation factors measurable in peripheral blood (19-20). Although FAR discriminated RPL from healthy early pregnancies with a high AUC in our cohort, its more modest AUC for distinguishing RPL from first-time miscarriage reflects a recurring theme in the literature: many mechanisms underlying a single spontaneous loss—such as embryonic aneuploidy, transient maternal inflammatory events, and localized placental developmental failure—overlap with those implicated in recurrent loss. Consequently, a nonspecific composite marker of inflammation and coagulation may detect biological abnormality without necessarily providing etiologic specificity among pathological miscarriage subgroups (3). This interpretive constraint suggests that FAR should be viewed as a screening or stratification marker rather than a definitive diagnostic tool. An elevated FAR should prompt follow-up testing, such as detailed thrombophilia screening, antiphospholipid antibody testing, cytogenetic analysis, and closer ultrasound surveillance; however, it should not be employed as the sole parameter for initiating invasive or long-term therapy without corroborating evidence (3). Practical concerns temper enthusiasm for immediate clinical implementation. While FAR is inexpensive and widely accessible, it is influenced by intercurrent infection, nutritional and hepatic status, and variations in inter-laboratory assay platforms. Furthermore, sampling at a single time point captures only a limited snapshot of maternal-fetal interactions, which evolve throughout the implantation and early placentation windows (20). Several single-center cohorts and retrospective analyses highlight heterogeneity in optimal FAR thresholds and AUC estimates—likely driven by laboratory variations in methodology, case-mix, gestational age at sampling, and

pre-analytical handling—underscoring the need for harmonized laboratory protocols and pre-specified analytic frameworks for external validation (21). Yes—large, multicenter prospective studies using standardized assays would be the appropriate next step to establish generalizable FAR cut-points, calibrate predictive values across populations, and determine the incremental value of FAR beyond routine clinical predictors. Combining FAR with orthogonal biomarkers and clinical variables may also improve discrimination. A multimarker model incorporating FAR with placental proteins such as placental growth factor, additional coagulation markers such as D-dimer, and detailed obstetric history could perform substantially better than any single biomarker alone. This integrated approach is broadly consistent with recent translational research and with recommendations from some guidelines supporting rigorously validated biomarker panels before clinical implementation (3-22). Mechanistic translational research remains equally important. Serial sampling across implantation and early placentation, together with proteomic analyses of placental and decidual tissues, may help clarify whether FAR primarily reflects causal pathological processes at the maternal-fetal interface or instead represents a downstream marker of heterogeneous upstream events. This distinction has important implications for intervention research and for determining whether FAR should be regarded solely as a marker or also as a potentially targetable biological signal (19,23,24).

The present study has several strengths, including the direct head-to-head comparison of RPL and first-time miscarriage groups within a narrowly defined early-pregnancy window, the use of routine and reproducible assays for fibrinogen and albumin, and transparent ROC reporting that facilitates comparison with other studies. Its principal limitations include the single-center design, which may limit external generalizability, the possibility of residual confounding from undetected comorbidities that may differentially affect albumin or fibrinogen levels, and the intrinsic nonspecificity of FAR as a general acute-phase and coagulation index. These limitations clearly support integrating FAR as one component of a broader diagnostic framework rather than using it as the sole basis for clinical decision-making. FAR is a biologically plausible composite biomarker and a practical tool that is elevated in RPL, with very good discriminatory ability for distinguishing RPL from healthy early pregnancy but only moderate ability for distinguishing recurrent from single-event miscarriage. The current evidence, including data from this cohort as well as from multiple independent single-center and proteomic studies, supports FAR as a promising screening marker that warrants harmonized multicenter validation and incorporation into multimarker predictive frameworks before routine clinical application (16).

The fibrinogen-to-albumin ratio (FAR) is a measurable composite biomarker that is typically elevated in women with recurrent pregnancy loss (RPL). In addition, FAR has shown good discriminatory ability for distinguishing RPL from healthy early pregnancy, although its performance in differentiating RPL from first-time miscarriage is only modest. These findings support the role of FAR as an inexpensive screening or risk-stratification tool that may help identify women who require further diagnostic evaluation or closer clinical surveillance. However, FAR should not be used in isolation to establish etiology or guide definitive therapy. Before it can be adopted into routine clinical practice, FAR requires external multicenter validation using standardized laboratory methods and should be evaluated within multimarker prediction models that integrate clinical history, immunothrombotic testing, and placental biomarkers.

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