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SERUM VASCULAR CELL ADHESION MOLECULE-1 AND THE DEPTH OF PLACENTAL INVASION IN PLACENTA ACCRETA SPECTRUM DISORDER: A CASE-CONTROL STUDY

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ABSTRACT

Background: Placenta accreta spectrum disorder (PASD) carries high maternal morbidity, yet no serum marker has entered clinical practice. Vascular cell adhesion molecule-1 (VCAM-1) mediates angiogenesis and trophoblast invasion, but whether its concentration tracks the depth of invasion is unknown.

Methods: In a case-control study at Haji Adam Malik General Hospital and the network hospitals of Universitas Sumatera Utara, Medan (March–September 2024), 31 women with PASD confirmed by post-hysterectomy histopathology and 32 women with normal pregnancy were recruited consecutively. Serum VCAM-1 was measured at least seven days before delivery. Groups were compared by the Welch t-test and invasion subgroups by ANOVA with the Tukey post-hoc test, with multivariable logistic regression and receiver operating characteristic analysis.

Results: VCAM-1 was higher in PASD than in normal pregnancy (435.35 ± 169.61 versus 293.12 ± 77.36 ng/mL; $p<0.001$) and rose across invasion depth — accreta 301.78 ± 72.16, increta 440.63 ± 196.09, percreta 518.21 ± 150.70 ng/mL ($p=0.007$) — with the post-hoc difference significant between accreta and percreta ($p=0.005$). After adjustment for maternal age and gestational age, VCAM-1 remained an independent predictor (adjusted odds ratio 2.97 per 100 ng/mL, 95% CI 1.52–5.80; $p=0.001$), and the area under the curve rose from 0.763 to 0.892. The Youden-optimal cut-off was 397 ng/mL (sensitivity 61.3%, specificity 93.8%).

Conclusion: Serum VCAM-1 is independently associated with PASD and increases with the depth of placental invasion, supporting further evaluation as an adjunct to prenatal ultrasound rather than as a stand-alone test.

Keywords: placenta accreta spectrum, vascular cell adhesion molecule-1, biomarkers, placentation, cesarean section

INTRODUCTION

Placenta accreta spectrum disorder (PASD) describes the abnormal adherence and invasion of placental tissue beyond the decidua basalis, encompassing placenta accreta, increta, and percreta according to the depth of myometrial penetration. It is one of the most consequential conditions in modern obstetrics because it may cause uterine rupture, catastrophic haemorrhage, loss of fertility, and maternal death.[1,2] The condition is rare in a first pregnancy and is widely regarded as iatrogenic in origin, being strongly associated with previous cesarean section (CS) and other procedures that disrupt the endometrial–myometrial interface.[3,4] As the availability of surgical delivery expands and maternal preference for CS increases, the number of CS procedures, and hence the burden of PASD, continues to rise.[5]

Indonesian data illustrate this trajectory. National figures for 2013 record approximately 927,000 of 4,039,000 deliveries (22.9%) as CS, and by 2019 the province with the highest proportion reaches 31.3%.[6,7] Because the incidence of PASD scales with the number of prior uterine scars, the epidemiological consequence for Indonesia over the coming decade is substantial.[8]

The clinical difficulty is that PASD is typically silent until the third stage of labour, when failure of placental separation or massive haemorrhage occurs.[1,9] Antenatal recognition therefore determines outcome, and prenatal ultrasound with the staging system of the International Federation of Gynecology and Obstetrics (FIGO) is the current mainstay.[10,11] Ultrasound is, however, operator-dependent, and its agreement with the histopathological grade obtained after delivery is imperfect, which has driven a search for objective

circulating markers. Candidates examined to date include vascular endothelial growth factor, placental growth factor, soluble Fms-like tyrosine kinase-1, pregnancy-associated plasma protein-A, and circulating microRNA, none of which has yet entered routine practice.[12–14]

Vascular cell adhesion molecule-1 (VCAM-1) is a calcium-independent transmembrane glycoprotein expressed on activated endothelium, tissue and placental macrophages, and trophoblast. Its transcription is induced principally by tumour necrosis factor-α and interleukin-1, and it mediates leukocyte adhesion and transendothelial migration as well as cell migration and invasion in tumour biology.[15] Within the uterus, VCAM-1 participates in placentation by promoting angiogenesis and trophoblast invasion and by mediating the interaction between maternal leukocytes and decidual cells with the invading trophoblast.[16] Given that excessive angiogenesis and unrestrained trophoblast invasion are the defining pathological features of PASD, VCAM-1 is a mechanistically plausible marker of the condition.[17,18]

Three previous studies support this hypothesis. Korkmazer et al. report increased placental VCAM-1 expression in morbidly adherent placenta, Mansour et al. describe higher serum and placental VCAM-1 in placenta accreta than in normal pregnancy, and Ersuz et al. identify VCAM-1 as the adhesion molecule most clearly elevated in placental invasion and adhesion anomalies.[16,19,20] What none of these studies has examined is whether VCAM-1 concentration is graded according to the anatomical depth of invasion — that is, whether it distinguishes accreta from increta and percreta rather than merely separating PASD from normal pregnancy. Such a gradient would be the strongest available evidence that circulating VCAM-1 reflects the severity of the invasive process rather than non-specific maternal inflammation. Data from Indonesian populations are also scarce, despite reference concentrations of soluble VCAM-1 in Indonesian pregnant women having been characterised locally.[21]

This study therefore aims to compare pre-delivery serum VCAM-1 concentrations between women with PASD and women with normal pregnancy, and to determine whether these concentrations differ according to the depth of placental invasion established by post-hysterectomy histopathology and by FIGO ultrasound stage.

METHODS

Study design and setting

This was a hospital-based case-control study conducted in the Department of Obstetrics and Gynecology of Haji Adam Malik General Hospital and the network hospitals of Universitas Sumatera Utara (USU), Medan, Indonesia, between March and September 2024. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[22] Ethical approval was granted by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (approval number 382/KEPK/USU/2024). Written informed consent was obtained from every participant before blood sampling.

Participants

Cases were pregnant women in whom PASD was suspected on prenatal ultrasound and subsequently confirmed histopathologically after hysterectomy, defined as villous tissue implanted beyond the decidua basalis. Eligible cases were aged 18 years or older, had a gestational age of at least 24 weeks at blood sampling, had complete medical records, and consented to participate. Women who elected fertility-sparing management, in whom hysterectomy and therefore histopathological confirmation were not performed, were excluded.

Controls were women with a normal singleton pregnancy delivered at the same institutions during the same period, in whom prenatal ultrasound showed normal placental implantation and in whom the placenta separated spontaneously and completely at delivery. Controls were selected to be broadly comparable to cases in terms of institution and calendar period. The following conditions were exclusion criteria in both groups, because each is independently associated with endothelial activation and would confound VCAM-1 interpretation: preeclampsia or other hypertensive disorder of pregnancy, gestational or pre-existing diabetes mellitus, clinically apparent infection including COVID-19, autoimmune or chronic inflammatory disease, chronic kidney disease, and active malignancy. Multiple pregnancy and fetal growth restriction were also excluded.

All eligible women presenting during the study window were enrolled consecutively. No formal a priori sample size calculation for a difference in means was performed; instead, a post-hoc power analysis was undertaken using the observed effect size and is reported below.

Laboratory measurement

Peripheral venous blood was collected at least seven days before delivery and, in every case, before any obstetric intervention. Samples were drawn into plain tubes, allowed to clot at room temperature, and centrifuged at 3,000 rpm for 10 minutes; the separated serum was stored at −80 °C until batch analysis. Serum VCAM-1 was quantified by sandwich enzyme-linked immunosorbent assay using the Human Vascular Cell Adhesion Molecule 1 (VCAM-1) ELISA Kit (catalogue number E0203Hu; BT LAB, Shanghai Korain Biotech Co., Ltd., Shanghai, China) following the manufacturer's instructions, with all samples assayed in duplicate and a standard curve generated for each assay run. Concentrations were expressed in ng/mL. Laboratory personnel were blinded to the clinical group of each sample.

Outcome definitions

The depth of invasion was graded on hysterectomy specimens as placenta accreta, increta, or percreta following the reporting recommendations of the international expert panel,[23] by a perinatal pathologist who had no access to the VCAM-1 results. Prenatal ultrasound findings were independently classified according to the FIGO staging system as PAS 1, PAS 2, or PAS 3 by an obstetrician experienced in placental

imaging who was blinded to both the histopathological [illegible] secondary outcome.

Statistical analysis

Analyses were performed in SPSS version 29 (IBM Corp., Armonk, NY, USA), with figures prepared in Python 3. Distributional normality was assessed by the Kolmogorov–Smirnov test and homogeneity of variance by Levene's test. Because the variances of VCAM-1 differed markedly between groups (Levene $p < 0.001$), the primary comparison used the Welch t-test rather than the Student t-test, with the Mann–Whitney test reported alongside it as a distribution-free confirmation. Continuous baseline variables were compared by the Welch t-test and categorical variables by the chi-square test, or Fisher's exact test where any expected cell count was below five. Differences in VCAM-1 across invasion subgroups were tested by one-way ANOVA with the Tukey honestly-significant-difference post-hoc procedure, and confirmed by the Kruskal–Wallis test.

Because maternal age and gestational age at sampling differed between groups, a multivariable binary logistic regression model was fitted with PASD as the dependent variable and VCAM-1, maternal age, and gestational age at sampling as covariates; the odds ratio for VCAM-1 was expressed per 100 ng/mL increment. Parity was not entered into the model because no case was primiparous, producing complete separation. [illegible]imination was assessed by the area under the [illegible]ver operating characteristic curve (AUC) for VCAM-[illegible]ne and for the fitted model, with 95% confidence intervals obtained by bias-corrected bootstrapping with 5,000 resamples. Candidate cut-offs were evaluated by the Youden index, and sensitivity, specificity, predictive values, accuracy, and positive likelihood ratio were reported for each. Agreement between FIGO stage and histopathological grade was quantified by Cohen's kappa and linearly weighted kappa. A pre-specified sensitivity analysis repeated the primary comparison after exclusion of extreme values. A two-sided p value below 0.05 was considered statistically significant.

RESULTS

Sixty-three women were analysed: 31 with histopathologically confirmed PASD and 32 with normal pregnancy. Baseline characteristics are shown in Table 1. Cases were older than controls (32.74 ± 4.23 versus 29.78 ± 4.53 years; $p = 0.009$) and were sampled at an earlier gestational age (34.97 ± 3.03 versus 37.28 ± 2.73 weeks; $p = 0.002$). Every case was non-primiparous, whereas seven controls (21.9%) were primiparous (Fisher's exact $p = 0.011$). Educational attainment did not differ between groups ($p = 0.706$), and the difference in the proportion aged over 30 years did not reach significance ($p = 0.055$). All women with PASD were delivered by cesarean hysterectomy.

Table 1. Baseline characteristics of cases and controls

Characteristic	PASD (n = 31)	Normal (n = 32)	p
Maternal age, years, mean ± SD	32.74 ± 4.23	29.78 ± 4.53	0.009[a]
Maternal age, median (range)	33 (24–40)	29 (23–38)	–
21–30 years, n (%)	10 (32.3)	19 (59.4)	0.055[b]
> 30 years, n (%)	21 (67.7)	13 (40.6)	
Gestational age at sampling, weeks	34.97 ± 3.03	37.28 ± 2.73	0.002[a]
Education, n (%)			0.706[b]
Elementary school	1 (3.2)	1 (3.1)	
Junior high school	3 (9.7)	4 (12.5)	
Senior high school	19 (61.3)	15 (46.9)	
Higher education	8 (25.8)	12 (37.5)	
Parity, n (%)			0.011[c]
Primiparous	0 (0)	7 (21.9)	
Non-primiparous	31 (100)	25 (78.1)	

Percentages are calculated within each group. [a]Welch t-test; [b]chi-square test; [c]Fisher's exact test. PASD: placenta accreta spectrum disorder; SD: standard deviation.

Serum VCAM-1 was substantially higher in cases than in controls (Table 2). The variances were unequal (Levene $p < 0.001$), and the Welch t-test gave $t = 4.26$ with $p < 0.001$; the Mann–Whitney test confirmed the difference ($p < 0.001$). The observed standardised effect size was large (Cohen $d = 1.09$), corresponding to a post-hoc statistical power of 98.9% at $\alpha = 0.05$ with the achieved sample of 31 and 32 participants; approximately 26 participants per group would have been required for 80% power. In the pre-specified sensitivity analysis excluding the two most extreme observations (540 ng/mL in a control and 102 ng/mL in a case), the difference was unchanged and slightly larger (446.47 ± 160.62 versus 285.16 ± 63.93 ng/mL; $p < 0.001$).

Table 2. Pre-delivery serum VCAM-1 concentration in cases and controls

Group	n	Mean ± SD (ng/mL)	Median (range)	p
PASD	31	435.35 ± 169.61	440 (102–750)	< 0.001
Normal pregnancy	32	293.12 ± 77.36	290 (141–540)	

Welch t-test (t = 4.26, df = 41.7); Mann–Whitney test p < 0.001. Levene's test for equality of variances p < 0.001. SD: standard deviation.

Among the 31 cases, histopathology showed placenta percreta in 14 (45.2%), placenta accreta in 9 (29.0%), and placenta increta in 8 (25.8%). On FIGO staging, 16 (51.6%) were classified as PAS 2, 9 (29.0%) as PAS 3, and 6 (19.4%) as PAS 1. VCAM-1 concentrations increased monotonically across both classifications (Table 3, Figure 1). For histopathological grade, ANOVA gave p = 0.007 and the Kruskal–Wallis test p = 0.003; the Tukey post-hoc procedure localised the difference to the comparison between accreta and percreta (mean difference 216.4 ng/mL, 95% CI 60.9–372.0; p = 0.005), whereas accreta versus increta (p = 0.146) and increta versus percreta (p = 0.469) did not reach significance. For FIGO stage, ANOVA gave p = 0.036 and the Kruskal–Wallis test p = 0.030, with the post-hoc difference confined to PAS 1 versus PAS 3 (mean difference 205.9 ng/mL, 95% CI 2.5–409.3; p = 0.047).

Table 3. Serum VCAM-1 according to depth of placental invasion and FIGO ultrasound stage

Subgroup	n	Mean ± SD (ng/mL)	Median (range)	p
Histopathological grade				0.007[a]
Placenta accreta	9	301.78 ± 72.16	283 (231–440)	0.003[b]
Placenta increta	8	440.63 ± 196.09	454.5 (102–697)	
Placenta percreta	14	518.21 ± 150.70	499 (282–750)	
FIGO ultrasound stage				0.036[a]
PAS 1	6	343.67 ± 128.02	285 (231–579)	0.030[b]
PAS 2	16	405.50 ± 174.70	384.5 (102–700)	
PAS 3	9	549.56 ± 132.85	532 (397–750)	

[a]One-way ANOVA; [b]Kruskal–Wallis test. Tukey post-hoc: accreta versus percreta p = 0.005; accreta versus increta p = 0.146; increta versus percreta p = 0.469; PAS 1 versus PAS 3 p = 0.047; PAS 1 versus PAS 2 p = 0.689; PAS 2 versus PAS 3 p = 0.086. FIGO: International Federation of Gynecology and Obstetrics; SD: standard deviation.

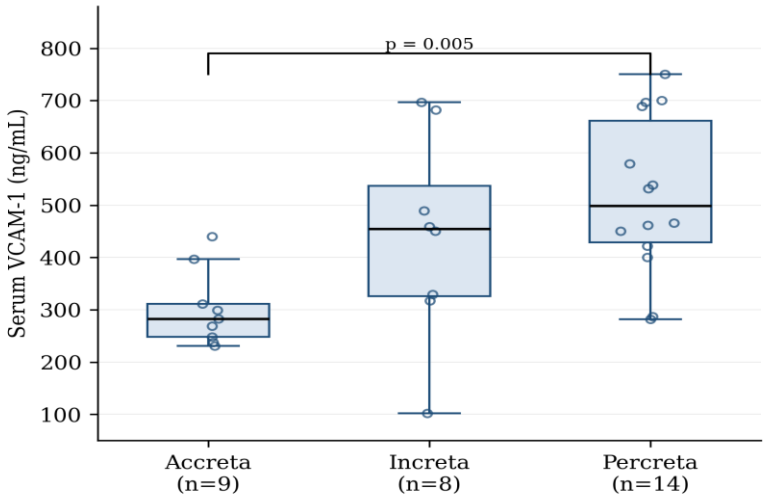


Figure 1. Distribution of pre-delivery serum VCAM-1 according to histopathological grade of invasion. Boxes show the median and interquartile range; whiskers extend to the most extreme values within 1.5 interquartile ranges; individual observations are overlaid. The bracket indicates the Tukey post-hoc comparison between accreta and percreta.

In the multivariable logistic regression model, VCAM-1 remained independently associated with PASD after adjustment for maternal age and gestational age at sampling (Table 4). Each increment of 100 ng/mL almost tripled the odds of PASD (adjusted odds ratio 2.97, 95% CI 1.52–5.80; p = 0.001). Maternal age was independently associated with PASD and gestational age at sampling inversely so. Notably, VCAM-1 was not correlated with gestational age within either group (cases r = 0.07, p = 0.707; controls r = 0.31, p = 0.089), indicating that the earlier sampling of cases does not account for their higher concentrations.

Table 4. Multivariable logistic regression for the presence of PASD

Variable	β (SE)	Adjusted OR (95% CI)	p
VCAM-1, per 100 ng/mL	1.088 (0.339)	2.97 (1.52–5.80)	0.001
Maternal age, per year	0.185 (0.079)	1.20 (1.03–1.41)	0.019
Gestational age, per week	−0.365 (0.144)	0.69 (0.52–0.92)	0.011

ot entered because no case was primiparous
ne. CI: confidence interval; OR: odds ratio; SE: standard error.

Discrimination is shown in Figure 2. VCAM-1 alone yielded an AUC of 0.763 (bootstrap 95% CI 0.631–0.877), and the adjusted model an AUC of 0.892. The Youden index was maximised at a cut-off of 397 ng/mL, which favoured specificity (61.3% sensitivity, 93.8% specificity, positive likelihood ratio 9.8); a lower threshold of 307 ng/mL balanced the two errors more evenly but performed less well overall (Table 5, Figure 3).

Table 5. Diagnostic performance of serum VCAM-1 at two candidate cut-offs

Cut-off	Sensitivity	Specificity	PPV	NPV	LR+
397 ng/mL[a]	61.3%	93.8%	90.5%	71.4%	9.8
307 ng/mL	71.0%	65.6%	66.7%	70.0%	2.1

[a]Youden-optimal cut-off (Youden index J = 0.55 versus 0.37 at 307 ng/mL). Overall accuracy 77.8% and 68.3%, respectively. LR+: positive likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

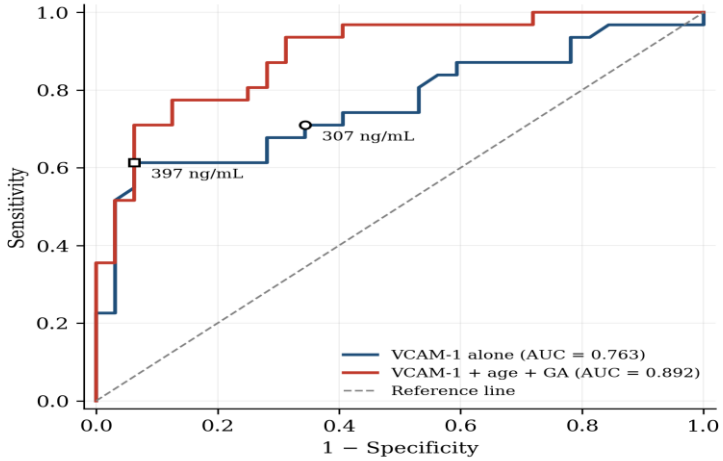


Figure 2. Receiver operating characteristic curves for pre-delivery serum VCAM-1 alone and for the multivariable model additionally including maternal age and gestational age at sampling. The two candidate cut-offs are marked. AUC: area under the curve; GA: gestational age.

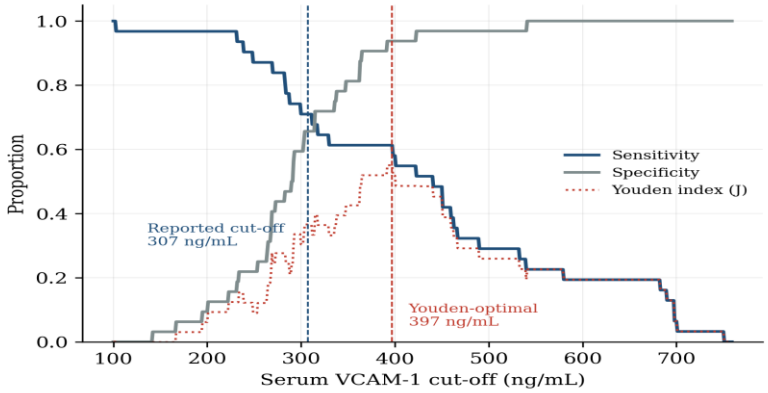


Figure 3. Sensitivity, specificity, and the Youden index across the range of candidate serum VCAM-1 cut-offs. The Youden index is maximised at 397 ng/mL

Agreement between the two severity classifications was modest (Table 6). Exact agreement occurred in 16 of 31 cases (51.6%), with Cohen's kappa 0.29 and linearly weighted kappa 0.24. Discordance ran in both directions: four women staged as PAS 1 had percreta at histopathology, while one woman staged as PAS 3 had only accreta.

Table 6. Agreement between FIGO ultrasound stage and histopathological grade among the 31 cases

Histopathological grade	PAS 1	PAS 2	PAS 3	Total
Placenta accreta	2	6	1	9
Placenta increta	0	7	1	8
Placenta percreta	4	3	7	14
Total	6	16	9	31

Exact agreement 51.6%; Cohen's kappa 0.29; linearly weighted kappa 0.24. FIGO: International Federation of Gynecology and Obstetrics.

DISCUSSION

This study shows that pre-delivery serum VCAM-1 is markedly higher in women with histopathologically confirmed PASD than in women with normal pregnancy, that the elevation is independent of maternal age and gestational age at sampling, and that concentrations increase with the anatomical depth of placental invasion. The last of these is, to our knowledge, the first such observation reported, and it is the finding with the clearest mechanistic implication.

The overall group difference confirms and extends earlier work. Korkmazer et al. demonstrate increased placental VCAM-1 expression in morbidly adherent placenta and, in a companion study, a parallel increase in intercellular adhesion molecule-1.[16,24] Mansour et al. report higher serum and placental VCAM-1 in placenta accreta than in normal pregnancy, and Ersuz et al. find VCAM-1 to be the most clearly elevated of five adhesion molecules in placental invasion and adhesion anomalies.[19,20] The magnitude of difference we observed is consistent with these reports, and the concentrations in our control group are compatible with reference values previously described in Indonesian pregnant women.[21]

The gradient across invasion depth is biologically coherent. Placenta percreta represents villous penetration through the full thickness of the myometrium to the serosa and, in advanced cases, into adjacent organs; it therefore entails the greatest degree of trophoblast invasion, neovascularisation, and disruption of the endothelial–decidual interface, all processes in which VCAM-1 is directly implicated.[15,17,18] That the post-hoc difference reaches significance only between accreta and percreta, with the intermediate increta group not separating from either, is what would be expected if VCAM-1 varies continuously with invasion depth while the histological categories divide that continuum coarsely; it may also simply reflect the small size of the increta subgroup (n = 8) and its wide dispersion. Whether circulating VCAM-1 originates predominantly from the invasive trophoblast, from activated endothelium at the implantation site, or from placental macrophages cannot be determined from serum measurement alone; recent single-cell work describing a loss of boundary limits between the decidua and the endothelium in PASD points to the implantation-site endothelium as one plausible source, and tissue-level studies will be needed to resolve this.[25]

Adjustment for confounders strengthens rather than weakens the association. Maternal age and gestational age at sampling both differ between our groups, as would be expected given that advanced maternal age is an established risk factor for PASD and that affected pregnancies are delivered earlier by design.[8,26] After adjustment, each 100 ng/mL increment in VCAM-1 is associated with a near-tripling of the odds of PASD, and the discrimination of the combined model (AUC 0.803) is numerically higher than that of VCAM-1 alone (AUC 0.737), although the difference is not statistically significant in this sample. The fact that the association survives adjustment for gestational age argues further against gestational timing as an explanation for the group difference.

The discrepancy between our cut-off and that of Mansour et al. (397 versus 79.89 ng/mL) deserves comment, because it is large and could otherwise be read as inconsistency. The most probable explanation is analytical rather than biological: absolute VCAM-1 concentrations are strongly assay-dependent, and different enzyme-linked immunosorbent assay kits, calibrators, and sample matrices yield values that differ by an order of magnitude and are not interchangeable across laboratories.[15] A secondary contributor is case mix. Nearly half of our cases have percreta, the grade with the highest concentrations, whereas the comparison study does not stratify by histopathological grade, so a cohort weighted towards accreta would be expected to produce a lower threshold. This is precisely why we report the internal gradient and the relative effect size in addition to an absolute cut-off: the former should be reproducible across laboratories, whereas the latter requires local assay-specific calibration before any clinical use.

Our secondary finding on classification agreement has practical relevance. Exact agreement between FIGO ultrasound stage and histopathological grade is only 51.6% (kappa 0.29), with four women staged as PAS 1 proving to have percreta. Imperfect concordance between prenatal imaging and pathology is recognised, and reflects both the operator dependence of ultrasound and the fact that the two systems grade different things — imaging appearance versus tissue penetration.[10,23] Rather than undermining the present analysis, this observation reinforces its rationale: if prenatal staging misclassifies the depth of invasion in nearly half of cases, an objective circulating marker that tracks invasion depth would add information that imaging alone does not provide. The practical corollary is that VCAM-1 should be evaluated as an adjunct to ultrasound rather than as a replacement for it.

Several limitations require emphasis. First, the case-control design with sampling after clinical suspicion had already arisen cannot establish that VCAM-1 elevation precedes or predicts PASD; a prospective cohort measuring VCAM-1 in unselected pregnancies with prior uterine scars is the necessary next step. Second, the cut-off values are derived and evaluated in the same 63 participants, so the reported sensitivity and specificity are optimistic and require external validation; our bootstrap confidence interval for the AUC (0.631–0.877) quantifies the imprecision but does not remove the optimism. Third, although the design excludes conditions known to activate endothelium, VCAM-1 is a non-specific marker of inflammation and endothelial dysfunction, being elevated

in preeclampsia, infection, and other inflammatory states,[21,26] so residual confounding from subclinical inflammation cannot be excluded and specificity in an unselected population would probably be lower than reported here. Fourth, subgroup sizes are small, particularly for increta (n = 8) and PAS 1 (n = 6), which limits the precision of the post-hoc comparisons. Fifth, other recognised determinants of outcome — birth weight, number of prior cesarean sections, and placenta previa — are not included in the multivariable model, and single-centre recruitment at a national referral hospital may have enriched the sample for severe disease, which would inflate apparent performance relative to a general obstetric population.

Set against these limitations, the study has genuine strengths. Every case is confirmed histopathologically rather than by imaging alone, avoiding the misclassification that weakens studies relying on ultrasound diagnosis; the two severity classifications are assigned independently and blinded to the biomarker result; the achieved sample provides 98.9% power for the primary comparison; and the analysis reports adjusted estimates, non-parametric confirmation, post-hoc comparisons, bootstrap confidence intervals, and a pre-specified sensitivity analysis rather than a single unadjusted test.

CONCLUSION AND RECOMMENDATION

Pre-delivery serum VCAM-1 is independently associated with placenta accreta spectrum disorder and rises with the anatomical depth of placental invasion, being highest in placenta percreta and in FIGO stage PAS 3. The stand-alone discrimination of the marker is moderate (AUC 0.763), which argues against its use as a single diagnostic test; combined with maternal age and gestational age, however, discrimination improved substantially (AUC 0.892), and at the Youden-optimal threshold of 397 ng/mL a positive result carried a positive likelihood ratio close to 10. VCAM-1 is therefore best positioned as a potential adjunct to prenatal ultrasound, particularly for flagging deeply invasive disease in women with sonographically equivocal findings.

Three lines of further work follow. Prospective cohort studies in women with prior uterine scars should determine whether VCAM-1 measured in the second trimester predicts subsequent PASD before imaging becomes diagnostic. Multicentre studies with harmonised assays are needed to establish transferable reference ranges and to validate cut-offs externally. Finally, combining VCAM-1 with ultrasound staging and with other candidate markers in a single prediction model, and including birth weight, number of previous cesarean sections, and placenta previa as covariates, would test whether the incremental value demonstrated here is retained in a fully specified model.

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AUTHOR CONTRIBUTIONS

DH conceived and designed the study, collected the data, performed the analysis, and drafted the manuscript. HPP supervised the study design, interpreted the laboratory findings, and critically revised the manuscript. MRT contributed to the interpretation of the results and critically revised the manuscript. All authors have read and approved the final version and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY

The de-identified dataset analysed in this study is available from the corresponding author on reasonable request.

ETHICAL APPROVAL AND CONSENT

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (approval number 382/KEPK/USU/2024), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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