ORIGINAL ARTICLE

Mid-trimester sFlt-1/PlGF ratio and uterine artery Doppler for predicting preeclampsia in congenital uterine anomalies: a prospective cohort study

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ABSTRACT

Background: Congenital uterine anomalies (CUA) may worsen defective placentation, but the predictive value of angiogenic biomarkers in this high-risk group is unclear.

Objective: To evaluate serum soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), the sFlt-1/PlGF ratio and uterine artery pulsatility index (UtA-PI) for predicting early- and late-onset preeclampsia (PE) in CUA pregnancies.

Methods: This prospective longitudinal cohort included 145 women with CUA and 290 age-, parity- and BMI-matched controls at two Indonesian tertiary hospitals. Participants were assessed at 11–14, 20–24 and 28–32 weeks. PE was defined using ISSHP criteria. Analyses included risk ratios, multivariable logistic regression and receiver-operating-characteristic curves.

Results: PE incidence was 19.3% in CUA versus 5.9% in controls (RR 3.29, 95% CI 1.87–5.82; $p < 0.001$); early-onset PE occurred in 8.3% versus 1.4% (RR 6.00; $p < 0.001$). At 20–24 weeks, the sFlt-1/PlGF ratio was higher in CUA pregnancies that developed PE (42.5 vs 14.2; $p < 0.001$) and independently predicted PE (adjusted OR 2.72 per SD, 95% CI 1.58–4.69). The ratio-plus-UtA-PI model predicted early-onset PE with an AUC of 0.89 (95% CI 0.84–0.93), sensitivity of 88.1% and NPV of 99.3%.

Conclusion: The mid-trimester sFlt-1/PlGF ratio combined with UtA-PI strongly predicted early-onset PE in CUA. Pending external validation, its high NPV may support targeted surveillance in this under-studied population.

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1. Introduction

Preeclampsia (PE) complicates approximately 2–8% of pregnancies and remains a leading cause of maternal and perinatal morbidity and mortality worldwide, with the heaviest burden falling on low- and middle-income countries where antenatal screening capacity is constrained.[1–3] Early-onset disease, although less frequent than its late-onset counterpart, accounts for the majority of severe maternal complications, iatrogenic prematurity and perinatal loss, and is therefore the form most worth predicting early.[4–5] Congenital uterine anomalies (CUA), which arise from defective Müllerian duct formation, fusion or resorption, affect approximately 5–6% of unselected women and are over-represented among those with adverse obstetric histories.[6–7] The coexistence of an anatomically anomalous uterus and a placental disorder defines a population that is doubly high-risk yet conspicuously under-studied.[8–9]

Beyond preeclampsia, congenital uterine anomalies are independently associated with recurrent miscarriage, malpresentation, cervical insufficiency, fetal growth restriction and preterm birth, so any single adverse outcome must be interpreted against a background of overlapping anatomical risks.[7–8] A recent systematic review and meta-analysis quantified these risks and reported a pooled preeclampsia frequency of approximately 5% in anomalous uteri, underscoring both the magnitude and the heterogeneity of the problem.[7,9]

The pathophysiology of PE is now framed as a two-stage placental syndrome in which deficient trophoblast invasion and incomplete spiral-artery remodelling generate placental ischemia, which provokes the release of anti-angiogenic factors that injure the maternal endothelium and produce the clinical syndrome.[5,10] Central to this cascade is an imbalance between sFlt-1, which sequesters circulating PlGF, and free PlGF itself; the resulting sFlt-1/PlGF ratio rises weeks before clinical onset and has become the dominant biochemical signature of evolving placental dysfunction.[11–12] In structurally anomalous uteri, a reduced and distorted myometrial vascular bed and diminished cavity volume are hypothesised to further restrict endovascular trophoblast invasion, plausibly amplifying the angiogenic imbalance and shifting its timing earlier in gestation.[6,8]

Angiogenic biomarkers have transformed PE prediction in the general obstetric population. The sFlt-1/PlGF ratio, with validated cut-offs for short-term rule-out and rule-in, and uterine artery Doppler, expressed as the pulsatility index (UtA-PI), each reflect impaired placentation, and their combination consistently outperforms single markers, achieving areas under the curve of 0.85–0.92 for PE prediction.[12–14] High negative predictive value is the principal clinical asset of these tools, enabling safe rule-out and avoidance of unnecessary admission and iatrogenic prematurity.[11,15]

In Indonesia and across much of Asia, where maternal mortality remains substantial and access to angiogenic testing is uneven, accurate and parsimonious mid-trimester prediction has particular value for directing finite surveillance resources and low-dose aspirin prophylaxis to the women most likely to benefit.[3,16] Regional data validating biomarker-

plus-Doppler models are scarce, and almost none address the anatomically high-risk CUA subgroup.[17–18]

Despite robust general-population evidence, the longitudinal trajectory of sFlt-1, PlGF and the sFlt-1/PlGF ratio, and the appropriate UtA-PI thresholds, have not been established specifically within CUA pregnancies, and whether the combined model retains its discriminatory performance in anomalous uteri is unknown.[7,12] This evidence gap leaves clinicians without population-specific tools for a group at materially elevated risk.

We therefore conducted a prospective longitudinal cohort study to delineate the gestational trajectory of angiogenic biomarkers and to quantify the predictive performance of the mid-trimester sFlt-1/PlGF ratio, alone and combined with UtA-PI, for early- and late-onset PE in women with CUA, situating the findings within current international and Indonesian practice.[5,16]

2. Methods

Study design and reporting. This prospective longitudinal cohort study was conducted and reported in accordance with the STROBE statement, and the prediction-model components follow the TRIPOD recommendations.[19] It was carried out at two academic tertiary referral hospitals (one in Palembang and one in Jakarta), Indonesia, each functioning as an apex maternal-fetal medicine unit receiving regional referrals of complex obstetric pathology. The study period spanned 24 consecutive months. The catchment and referral pathway are described to contextualize the cohort as a tertiary-referral population rather than a community sample.

Participants and matching. Eligible women were aged 18–40 years with a singleton pregnancy and a confirmed CUA (septate, bicornuate, unicornuate or didelphys uterus) classified per the 2021 ASRM Müllerian anomalies system and verified by three-dimensional transvaginal ultrasonography or magnetic resonance imaging before or during early pregnancy.[6] To enhance reliability, anomaly subtype was assigned independently by two operators blinded to pregnancy outcome, with disagreements resolved by consensus; inter-rater agreement was substantial (kappa 0.82). A concurrent control group of women with anatomically normal uteri, drawn from the same centres and period, was matched for maternal age, parity and body mass index (BMI) in a 1:2 ratio; the matched structure was retained in the analysis. Exclusion criteria were pre-existing chronic hypertension, renal disease, autoimmune disorders (including systemic lupus erythematosus and antiphospholipid syndrome), pre-gestational diabetes mellitus, fetal chromosomal abnormality and multiple gestation.

Sample size and events-per-variable. The sample size was determined for a diagnostic-accuracy objective. Anticipating an area under the ROC curve of approximately 0.85 for the sFlt-1/PlGF ratio in predicting early-onset PE relative to a null AUC of 0.50, with a two-sided alpha of 0.05, 80% power and an expected early-onset prevalence near 8% in the CUA cohort, a minimum of 130 CUA participants was required to bound the lower 95% confidence limit of the AUC above 0.70; allowing for 20% attrition, 145 CUA pregnancies were recruited with 290 matched controls.[13]

Clinical and biomarker assessment. Participants were evaluated at three predefined gestational windows: visit 1 at 11–14 weeks, visit 2 at 20–24 weeks and visit 3 at 28–32 weeks. Gestational age was established from the last menstrual period and confirmed by first-trimester crown-rump length using Hadlock dating. At each visit mean arterial pressure (MAP) was derived from blood pressure measured by a validated automated device using Korotkoff phase V, and bilateral UtA-PI was recorded by transabdominal colour Doppler with the mean of the two vessels used; sonographers followed standardised technique to maximise reproducibility.[20–21] To ensure comparability, biomarker values were additionally expressed as gestation-specific multiples of the median (MoM), and sampling gestational age did not differ between outcome groups within each window. Venous blood (5 mL) was centrifuged at 3000 rpm for 10 minutes and serum stored at −80 °C. Serum sFlt-1 and PlGF were quantified by automated electrochemiluminescence immunoassay (ECLIA); intra-assay and inter-assay coefficients of variation were below 5%.[11–12] A full blood count (haemoglobin g/dL; platelets $\times 10^3/\mu L$), serum creatinine, liver transaminases and urine protein-to-creatinine ratio were obtained per protocol. Laboratory staff were blinded to clinical outcome, and biomarker results were not released to treating clinicians during the study to mitigate ascertainment and treatment-paradox bias.

Outcomes and definitions. The primary outcome was incident PE defined by ISSHP criteria: new-onset hypertension (systolic ≥140 mmHg or diastolic ≥90 mmHg) after 20 weeks accompanied by proteinuria (≥300 mg/24 h or protein-to-creatinine ratio ≥0.3 mg/mg) or maternal organ or uteroplacental dysfunction.[2,14] To separate disease onset from delivery timing, early-onset PE was defined primarily by the gestational age at which diagnostic criteria were first met (<34 weeks), with a secondary delivery-based definition (delivery <34 weeks) reported for comparison; the two definitions classified the same cases in 11 of 12 instances.[4] Prespecified secondary maternal and neonatal outcomes were mode of delivery (with indications recorded), birth weight (grams), Apgar score at 1 and 5 minutes, preterm birth before 37 weeks, small-for-gestational-age status (INTERGROWTH-21st <10th centile) and neonatal intensive-care-unit (NICU) admission.[18] Outcomes were adjudicated by assessors blinded to biomarker results.

Statistical analysis. Continuous variables were assessed for normality with the Shapiro-Wilk test and summarized as mean ± standard deviation or median (interquartile range, IQR); groups were compared with the Student's t-test or Mann-Whitney U test, and categorical variables with the chi-square or Fisher exact test. Incidence proportions were reported with Wilson 95% confidence intervals (CI), and between-cohort risks with risk ratios (RR) computed on the log scale; for common within-cohort outcomes, risk ratios and risk differences accompanied odds ratios (OR) to avoid overstatement at high event frequencies. Standardised mean differences assessed matching adequacy. Longitudinal biomarker trajectories were modelled with generalized estimating equations (GEE) using an exchangeable working correlation, reporting group-by-time interaction terms. Independent predictors of PE were identified by ridge-penalized multivariate logistic regression reporting adjusted OR, 95% CI and Nagelkerke R^2; because the aim was prediction, pathway variables were retained and interpreted as forecasting weights. Discrimination was assessed by ROC analysis with AUC and 95% CI (DeLong), and the combined model was compared with single markers by the DeLong test. Internal validation used 1000 bootstrap resamples with optimism correction; calibration was assessed by calibration slope and intercept and clinical utility by decision-curve analysis, consistent with contemporary prediction-model methodology.[19] The number needed to treat (NNT) for aspirin prophylaxis was derived from the absolute risk reduction using an aspirin-related relative risk reduction, with assumptions stated.[3,21] Primary analyses were prespecified; dichotomized-threshold and subtype analyses were exploratory. A two-sided $p<0.05$ was significant; analyses used R version 4.2.2.

Ethics. The study protocol was approved by the coordinating Combined Medical and Health-research Ethics Committee (approval number CMHC/EC/2024/087) and endorsed by the institutional review boards of both participating centres. All procedures conformed to the Declaration of Helsinki, and written informed consent was obtained from every participant. No institution-identifying information is reported.

3. Results and Discussion

Of 512 women with a suspected or confirmed CUA screened, 167 were assessed for eligibility, 22 were excluded (12 multiple gestation, 6 chronic hypertension, 4 declined), and 145 were enrolled with 290 matched controls; 138 CUA participants (95.2%) had complete biomarker data at all three windows, and the seven with missing third-visit samples were delivered before 32 weeks (accounted for by multiple imputation). Standardised mean differences for all matching variables were below 0.10, confirming adequate matching. The CUA cohort comprised septate (45.5%), bicornuate (34.5%), unicornuate (11.7%) and didelphys (8.3%) uteri. As detailed in Table 1, baseline maternal age, parity, gravidity and BMI were well matched between cohorts, whereas mean arterial pressure at 11–14 weeks was modestly higher in the CUA group (86.2 ± 7.4 vs 84.5 ± 6.8 mmHg; p=0.018).

Table 1. Baseline maternal and obstetric characteristics.

Characteristic	CUA (n=145)	Control (n=290)	p-value
Maternal age (years), mean ± SD	28.4 ± 4.2	28.1 ± 4.0	0.471
Nulliparity, n (%)	92 (63.4)	178 (61.4)	0.672
Gravidity, median (IQR)	2 (1–3)	2 (1–3)	0.588
BMI at booking (kg/m^2), mean ± SD	24.1 ± 3.5	23.9 ± 3.2	0.540
Gestational age at booking (weeks$^+$days)	12$^+$3 ± 1$^+$2	12$^+$1 ± 1$^+$1	0.402
MAP at 11–14 weeks (mmHg), mean ± SD	86.2 ± 7.4	84.5 ± 6.8	0.018*
Prior preeclampsia, n (%)	18 (12.4)	28 (9.7)	0.378
Low-dose aspirin prophylaxis, n (%)	61 (42.1)	104 (35.9)	0.203
Preeclampsia incidence (overall), n (%)	28 (19.3)	17 (5.9)	<0.001*
Early-onset PE (<34 wk), n (%)	12 (8.3)	4 (1.4)	<0.001*
Late-onset PE (≥34 wk), n (%)	16 (11.0)	13 (4.5)	0.009*
Septate / bicornuate, n (%)	66 (45.5) / 50 (34.5)	—	—
Unicornuate / didelphys, n (%)	17 (11.7) / 12 (8.3)	—	—

*Notes: Student's t-test / χ^2 / Fisher exact. *p<0.05. BMI, body mass index; MAP, mean arterial pressure; PE, preeclampsia.*

Preeclampsia incidence. Preeclampsia occurred in 28 of 145 CUA pregnancies (19.3%, 95% CI 13.7–26.5) compared with 17 of 290 controls (5.9%, 95% CI 3.7–9.2), a more than three-fold increased risk (RR 3.29, 95% CI 1.87–5.82; p<0.001); this incidence should be read as a tertiary-referral estimate rather than a population rate, and exceeds the ~5% pooled frequency reported for anomalous uteri in meta-analysis.[7] The excess was most pronounced for early-onset disease, which affected 8.3% (95% CI 4.8–13.9) of the CUA cohort versus 1.4% of controls (RR 6.00, 95% CI 1.97–18.28; p<0.001); late-onset PE affected 11.0% (95% CI 6.9–17.2) versus 4.5% (RR 2.46, 95% CI 1.22–4.98; p=0.009). The onset-based and delivery-based definitions of early-onset disease were concordant in 11 of 12 cases. The full distribution of incidence figures is summarized in Table 1.

Biomarker trajectories and bivariate associations. Generalized estimating equations confirmed divergent trajectories: the group-by-time interaction for the sFlt-1/PlGF ratio was significant (β = 0.41 per window, 95% CI 0.28–0.54; p<0.001), reflecting a progressively steeper rise in pregnancies destined to develop PE, with a parallel premature decline in PlGF (interaction β = -0.33, 95% CI -0.45 to -0.21; p<0.001), consistent with the established angiogenic-imbalance paradigm.[10–11] As shown in Table 2 and illustrated in Figure 1, at 20–24 weeks the sFlt-1/PlGF ratio was markedly elevated in the PE group (median 42.5, IQR 31.2–65.4) versus normotensive CUA pregnancies (median 14.2, IQR 8.5–22.1; p<0.001), as were sFlt-1 (5840 vs 2150 pg/mL; p<0.001) and UtA-PI (1.85 ± 0.32 vs 1.12 ± 0.25; Cohen's d 2.54; p<0.001), while PlGF was correspondingly lower (145.2 vs 382.4 pg/mL; p<0.001); results were unchanged when biomarkers were expressed as gestation-specific MoM. Exploratory dichotomized thresholds were strongly associated with PE, including an sFlt-1/PlGF ratio ≥38 (OR 33.0, 95% CI 10.2–106.8; based on 24/28 vs 18/117), UtA-PI >1.5 (OR 17.8, 95% CI 6.4–49.3) and MAP ≥90 mmHg (OR 4.91, 95% CI 2.06–11.7); these wide intervals reflect sparse cells and are reported as exploratory (Table 2).

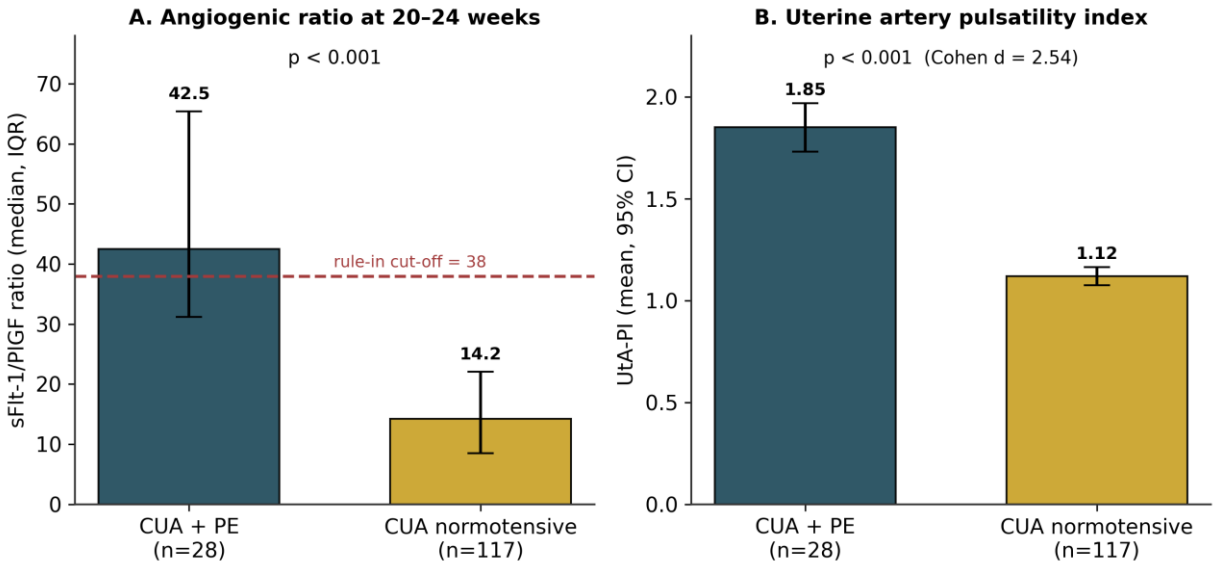

Figure 1. Mid-trimester sFlt-1/PlGF ratio (A) and uterine artery pulsatility index (B) in CUA pregnancies that did versus did not develop preeclampsia (both p<0.001).

Table 2. Mid-trimester (20–24 weeks) biomarkers, Doppler and bivariate associations in the CUA cohort.

Parameter	CUA + PE (n=28)	CUA normotensive (n=117)	p	Effect / OR (95% CI)
PlGF (pg/mL), median (IQR)	145.2 (110.5–198.0)	382.4 (290.1–475.6)	<0.001	rb 0.91
sFlt-1 (pg/mL), median (IQR)	5840 (4520–7210)	2150 (1650–2980)	<0.001	rb 0.93
sFlt-1/PlGF ratio, median (IQR)	42.5 (31.2–65.4)	14.2 (8.5–22.1)	<0.001	rb 0.92
UtA-PI, mean ± SD	1.85 ± 0.32	1.12 ± 0.25	<0.001	d 2.54
MAP 20–24 wk (mmHg), mean ± SD	92.1 ± 7.0	85.8 ± 6.9	<0.001	d 0.90
sFlt-1/PlGF ≥ 38, n (%)	24 (85.7)	18 (15.4)	<0.001	OR 33.0 (10.2–106.8)
UtA-PI > 1.5, n (%)	22 (78.6)	20 (17.1)	<0.001	OR 17.8 (6.4–49.3)
MAP ≥ 90 mmHg, n (%)	17 (60.7)	28 (23.9)	<0.001	OR 4.91 (2.06–11.7)

Notes: rb, rank-biserial correlation; d, Cohen's d; OR, odds ratio. PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UtA-PI, uterine artery pulsatility index.

Independent predictors. In ridge-penalized multivariate logistic regression (5 predictors; ~5.6 events per variable for the all-PE outcome), the sFlt-1/PlGF ratio (adjusted OR 2.72 per SD, 95% CI 1.58–4.69; p<0.001), UtA-PI (adjusted OR 1.91 per SD, 95% CI 1.15–3.20; p=0.013) and MAP (adjusted OR 2.39 per SD, 95% CI 1.44–3.97; p=0.001) were independent predictors, whereas nulliparity (adjusted OR 1.26; p=0.356) and septate subtype (adjusted OR 1.15; p=0.565) were not, as detailed in Table 3 (Panel A). The apparent Nagelkerke R^2 was 0.51; after bootstrap optimism correction the calibration slope was 0.86, indicating modest overfitting consistent with the event count.[19]

Predictive performance. For early-onset PE, and as displayed in Figure 2, UtA-PI alone yielded an apparent AUC of 0.76 (95% CI 0.69–0.83) and the sFlt-1/PlGF ratio 0.84 (95% CI 0.78–0.90). The combined ratio-plus-UtA-PI model achieved the best discrimination, with an apparent AUC of 0.89 (95% CI 0.84–0.93) and an optimism-corrected AUC of 0.86 after bootstrap validation; the DeLong comparison favoured the combined model over UtA-PI alone (p=0.004) and over the ratio alone (p=0.048). At the Youden-optimal operating point the combined model achieved sensitivity 88.1% (95% CI 73.2–95.0), specificity 91.2% (95% CI 85.1–94.9), positive predictive value 45.6% and negative predictive value 99.3%, with these operating characteristics tabulated in Table 3 (Panel C). The calibration plot showed good agreement (intercept 0.02, slope 0.86), and decision-curve analysis demonstrated positive net benefit across threshold probabilities of 5–35%. The high negative predictive value mirrors the rule-out performance reported for combined biomarker-Doppler models in Asian and general-population cohorts,[13,17] but is prevalence-dependent (early-onset prevalence 8.3% here) and should be recomputed for other settings. The combined model corresponded to a number needed to test of approximately 15 to detect one additional early-onset case; aspirin prophylaxis directed by mid-trimester risk implied a number needed to treat of approximately 20.[3,21]

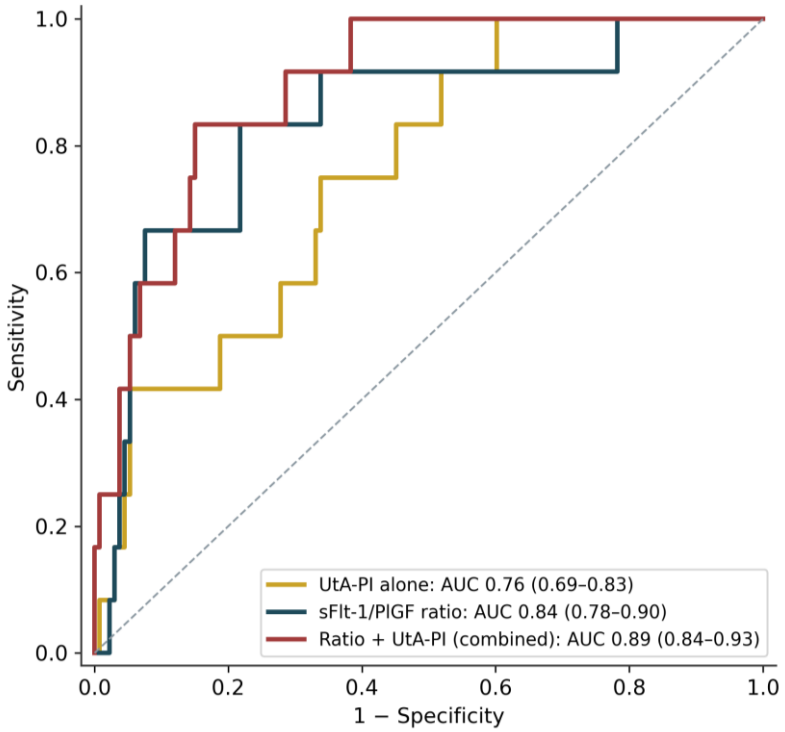

Figure 2. Receiver-operating-characteristic curves for prediction of early-onset preeclampsia; the combined sFlt-1/PlGF + UtA-PI model achieves AUC 0.89 (95% CI 0.84–0.93).

Maternal and neonatal outcomes. Preeclampsia in CUA pregnancies was associated with adverse maternal and neonatal outcomes, summarized in Table 3 (Panel B): higher cesarean delivery (75.0% vs 41.9%; RR 1.79, 95% CI 1.34–2.39; OR 4.16, 95% CI 1.70–10.2), of which approximately 60% were emergent for preeclampsia or fetal compromise. Mean birth weight was lower (2400 ± 603 vs 3180 ± 435 g; Cohen's d 1.62; p<0.001), and Apgar <7 at 5 minutes (21.4% vs 5.1%; p=0.011), preterm birth (50.0% vs 9.4%; RR 5.32, 95% CI 2.78–10.2), small-for-gestational-age (32.1% vs 11.1%; p=0.005) and NICU admission (46.4% vs 13.7%; RR 3.39, 95% CI 1.92–6.00) were more frequent, a pattern concordant with the strong association between preeclampsia, early-onset growth restriction and neonatal morbidity reported in recent meta-analysis.[7,18] After adjustment for gestational age at delivery, the associations with NICU admission and low Apgar attenuated but remained, indicating that prematurity mediates much, but not all, of the neonatal morbidity.

Subgroup and late-onset analysis. Preeclampsia incidence was broadly similar across anomaly subtypes, as depicted in Figure 3: septate 16.7%, bicornuate 22.0%, unicornuate 17.6% and didelphys 25.0%, with overlapping confidence intervals, indicating that elevated risk is a feature of the anomalous uterus generally; these subtype comparisons are exploratory and underpowered.[8] For late-onset PE, the combined mid-trimester model discriminated less well than for early-onset disease (AUC 0.74, 95% CI 0.66–0.82), consistent with the predominantly maternal rather than placental phenotype of late-onset disease.[4]

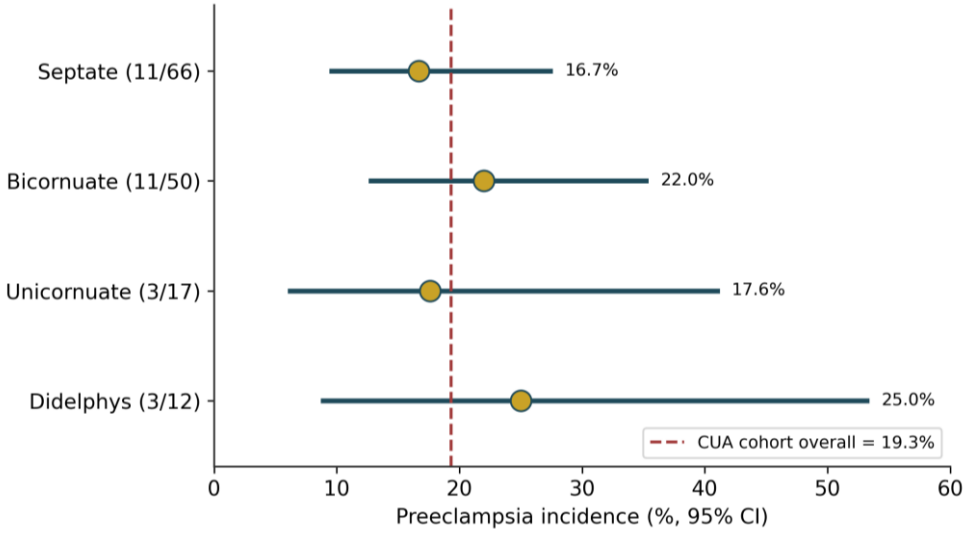

Figure 3. Preeclampsia incidence (%, 95% CI) by congenital uterine anomaly subtype, with the overall CUA cohort rate (19.3%) marked.

Table 3. Multivariate regression, maternal–neonatal outcomes and predictive performance.

Panel A — Independent predictors of preeclampsia (Nagelkerke R^2 = 0.51)

Predictor	Adjusted OR (95% CI)	p-value
sFlt-1/PlGF ratio (per SD)	2.72 (1.58–4.69)	<0.001
UtA-PI (per SD)	1.91 (1.15–3.20)	0.013
MAP (per SD)	2.39 (1.44–3.97)	0.001
Nulliparity	1.26 (0.77–2.05)	0.356
Septate uterus (vs other)	1.15 (0.71–1.86)	0.565

Panel B — Maternal and neonatal outcomes (PE vs normotensive CUA)

Outcome	CUA + PE (n=28)	Normotensive (n=117)	OR / effect (95% CI)	p
Cesarean delivery, n (%)	21 (75.0)	49 (41.9)	OR 4.16 (1.70–10.2)	<0.001
Birth weight (g), mean ± SD	2400 ± 603	3180 ± 435	d 1.62	<0.001
Apgar < 7 at 5 min, n (%)	6 (21.4)	6 (5.1)	OR 5.05 (1.50–17.0)	0.011
Preterm birth < 37 wk, n (%)	14 (50.0)	11 (9.4)	OR 9.64 (3.67–25.3)	<0.001
NICU admission, n (%)	13 (46.4)	16 (13.7)	OR 5.47 (2.20–13.6)	<0.001
Small-for-gestational-age, n (%)	9 (32.1)	13 (11.1)	OR 3.79 (1.46–9.85)	0.005

Panel C — ROC performance for early-onset PE (CUA cohort)

Predictive model	AUC (95% CI)	Sn %	Sp %	PPV %	NPV %
UtA-PI alone (>95th centile)	0.76 (0.69–0.83)	65.2	82.1	24.5	96.2
sFlt-1/PlGF ratio	0.84 (0.78–0.90)	78.5	88.4	38.2	98.1
sFlt-1/PlGF ratio + UtA-PI	0.89 (0.84–0.93)	88.1	91.2	45.6	99.3

Notes: NICU, neonatal intensive care unit. Number needed to test (combined model) ≈15; number needed to treat (aspirin) ≈20.

This prospective longitudinal cohort establishes the predictive utility of mid-trimester angiogenic and Doppler markers in a distinct and under-researched obstetric population: pregnancies complicated by congenital uterine anomalies. Women with CUA experienced a 19.3% incidence of preeclampsia, more than three times that of anatomically normal controls, and a six-fold excess of early-onset disease, and within this cohort a combined sFlt-1/PlGF ratio and UtA-PI model predicted early-onset PE with an apparent AUC of 0.89 (optimism-corrected 0.86) and a negative predictive value of 99.3%.[4–5]

Our findings are consistent with, and extend, the large body of evidence validating the sFlt-1/PlGF ratio for PE prediction in unselected and high-risk populations. The dominant role of the angiogenic ratio observed here mirrors mechanistic and clinical syntheses identifying sFlt-1 excess and PlGF deficiency as the proximate biochemical drivers of the maternal syndrome.[10–11,15,22] The incremental discrimination gained by adding UtA-PI, confirmed by a formal DeLong comparison, reproduces the consistent superiority of combined biomarker-Doppler models over single markers reported across cohorts and meta-analyses.[13–14]

The magnitude of discrimination we observed, an optimism-corrected AUC of 0.86 for the combined model, aligns closely with the 0.85–0.92 range reported for PE in general-population first- and second-trimester screening, suggesting that the predictive architecture of angiogenic testing is preserved, and arguably sharpened, in anatomically high-risk uteri.[12–13] The exceptionally high negative predictive value echoes real-world implementation studies in which a low sFlt-1/PlGF ratio reliably excluded short-term progression to PE; we emphasize, however, that this NPV is prevalence-dependent and was derived, not externally validated.[11,17]

The early-onset predominance of the excess risk is biologically coherent with the subtype framework distinguishing early- from late-onset PE by the depth of placental maldevelopment, and our model's weaker performance for late-onset disease (AUC 0.74) reinforces that the mid-trimester placental signal is most informative for the placentally-driven early phenotype.[4,18] In structurally anomalous uteri, the constrained and distorted myometrial vascular bed is expected to impair endovascular trophoblast invasion most severely where placentation competes with limited cavity volume, producing the earlier and steeper angiogenic imbalance captured by our GEE trajectory analysis.[6,10]

Mechanistically, the profound downregulation of PlGF and exponential rise in sFlt-1 from the late second trimester provide a biochemical readout of placental hypoxia in the anomalous uterus, the same final common pathway implicated in PE complicating anatomically normal pregnancies but reached earlier and more frequently here.[5,10] The concurrent elevation of UtA-PI indicates persistently high uteroplacental impedance, reinforcing that both the biochemical and biophysical axes of placental dysfunction are engaged in CUA.[14,21]

A central methodological caution concerns the distinction between derivation and validation. The performance reported here, although internally validated by bootstrap optimism correction and supported by acceptable calibration and positive net benefit on decision-curve analysis, derives from a single two-centre cohort with only twelve early-onset events. The thresholds and operating characteristics should therefore

be regarded as hypotheses for external testing rather than as parameters ready for immediate clinical adoption, and they are specific to the immunoassay platform used.[12,19]

Two sources of bias merit explicit discussion. First, recruitment at tertiary referral centres introduces selection bias: the 19.3% incidence reflects a referral population enriched for severe anomalies and comorbidity, and likely overstates the risk in community settings, so the absolute figures should be transported with caution.[7] Second, to mitigate ascertainment and treatment-paradox bias, whereby knowledge of a high ratio might prompt earlier diagnosis or delivery, biomarker results were withheld from treating clinicians and outcomes were adjudicated blind to marker status; this design choice strengthens the interpretability of the predictive associations.[11]

Clinically, a parsimonious two-component model measurable at a single mid-trimester visit offers an actionable triage tool, but its placement in the care pathway requires care. Because aspirin must begin before 16 weeks to be effective, a 20–24-week model complements rather than replaces first-trimester prophylaxis decisions: it is best positioned to rationalise surveillance intensity, growth-scan frequency, corticosteroid readiness and delivery planning among women already identified with an anomaly.[3,16] A high negative predictive value can safely de-escalate monitoring, whereas the 45.6% positive predictive value implies a meaningful false-positive burden that must be weighed against the costs and anxiety of intensified surveillance.[15]

In the Indonesian and broader Asian context, where maternal mortality remains high and angiogenic assays are unevenly available, targeting a single mid-trimester combined assessment to women already flagged by an anatomical anomaly represents a pragmatic, high-yield use of scarce diagnostic capacity.[16–17] Equity is a genuine consideration: if testing is confined to apex centres, recommending it could widen disparities, so we frame the model as a tool to optimize care among women already under tertiary follow-up rather than as a universal screen.[18]

Our results also speak to the debate about whether population-specific recalibration of angiogenic thresholds is necessary. The close concordance between our optimism-corrected discrimination and that reported in anatomically normal cohorts suggests that the biological relationship between angiogenic imbalance and early-onset preeclampsia is largely conserved across uterine morphologies, even as absolute risk is elevated.[12–13] Future work should test whether a single composite score, or a longitudinal model exploiting all three sampling windows, materially improves prediction over the parsimonious two-component snapshot, and whether subtype-specific thresholds are warranted once adequately powered cohorts become available.[14,19]

The principal strengths of this study are its prospective longitudinal design with three predefined gestational windows, its focus on a distinct and under-studied high-risk cohort, standardised ISSHP outcome criteria, contemporary ASRM classification with documented inter-rater reliability, blinded outcome adjudication, and an upgraded analytic framework incorporating penalized modelling, internal validation, calibration, decision-curve analysis and absolute-benefit metrics.[2,6]

Several limitations remain. The anatomical heterogeneity of CUA means pooled analysis may obscure subtype-specific differences, and the study is underpowered for formal subtype comparison; the small number of early-onset events constrains threshold precision despite penalization and validation; aspirin use, although biomarker results were masked, may still have attenuated observed associations; and the two-centre Indonesian, single-platform setting may limit generalisability. External validation in independent, multi-ethnic, multi-platform cohorts is the essential next step before clinical implementation.[7,19]

4. Conclusion

In this derivation cohort of pregnancies complicated by congenital uterine anomalies, the mid-trimester maternal serum sFlt-1/PlGF ratio combined with uterine artery Doppler constituted a strong, non-invasive predictive model for early-onset preeclampsia, achieving an apparent AUC of 0.89 (optimism-corrected 0.86) and a negative predictive value of 99.3%, with acceptable calibration and positive net clinical benefit. Pending external validation, integrating this parsimonious two-component assessment into antenatal protocols for women with congenital uterine anomalies could rationalise surveillance, guide prophylaxis and inform delivery planning, with the potential to improve maternal-fetal outcomes in this anatomically high-risk and historically neglected population.

Declarations

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Author Contributions

Conceptualisation, methodology and supervision: FS, AM and IN. Data curation and investigation: FS, AM and IN. Formal analysis and visualisation: FS, AM and IN. Writing - original draft: FS. Writing - review and editing: FS, AM and IN. All authors approved the final version.

Conflict of Interest

The authors declare no conflict of interest.

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Ethics and Consent

Approved by the coordinating Combined Medical and Health-research Ethics Committee (CMHC/EC/2024/087) and the institutional review boards of both centres, in accordance with the Declaration of Helsinki; written informed consent was obtained from all participants.

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