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ORIGINAL RESEARCH

Prognostic Value of Angiogenic Markers in Pregnant Women With Chronic Hypertension

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BACKGROUND: Women with chronic hypertension face a 5- to 6-fold increased risk of developing preeclampsia compared with normotensive women. Angiogenic markers, especially soluble fms-like kinase 1 (sFlt-1) and placental growth factor (PlGF), were identified as clinically useful markers predicting the development of preeclampsia, but data on the prediction of superimposed preeclampsia are scarce. Therefore, we aimed to evaluate the predictive value of the sFlt-1/PlGF ratio for delivery because of superimposed preeclampsia in women with chronic hypertension.

METHODS AND RESULTS: This retrospective study included 142 women with chronic hypertension and suspected superimposed preeclampsia. Twenty-seven women (19.0%) delivered because of maternal indications only, 17 women (12.0%) because of fetal indications primarily, and 98 women (69.0%) for other reasons. Women who both delivered because of maternal indications and for fetal indications had a significantly higher sFlt-1/PlGF ratio (median 99.9 and 120.2 versus 7.3, respectively, $P<0.001$ for both) and lower PlGF levels (median 73.6 and 53.3 versus 320.0 pg/mL, respectively, $P<0.001$ for both) compared with women who delivered for other reasons. SFlt-1/PlGF ratio and PlGF were strong predictors for delivery because of superimposed preeclampsia, whether for maternal or fetal indications ($P<0.05$). Half of women with angiogenic imbalance (sFlt-1/PlGF ratio ≥85 or PlGF levels <100 pg/mL) delivered because of maternal or fetal indications within 1.6 weeks (95% CI, 1.0–2.4 weeks).

CONCLUSIONS: Angiogenic marker imbalance in women with suspected superimposed preeclampsia can predict delivery because of maternal and fetal indications related to superimposed preeclampsia and is associated with a significantly shorter time to delivery interval.

Key Words: angiogenic markers ■ chronic hypertension ■ preeclampsia ■ superimposed preeclampsia

Preeclampsia is one of the leading causes of maternal and perinatal mortality and morbidity worldwide, with chronic hypertension being one of the most important risk factors.[1,2] Up to 1 of 4 women with chronic hypertension develop preeclampsia during the antenatal period. Women with chronic hypertension are at 5- to 6-fold increased risk of developing preeclampsia compared with normotensive women.[3–6] A meta-analysis of pregnant women with chronic hypertension and adverse outcomes, comprising ≈800 000 pregnancies, concluded that chronic hypertension is associated with a higher risk of superimposed preeclampsia, preterm birth, birth weight <2500 g, higher rate of cesarean delivery, neonatal unit admission, and perinatal death.[1] The best method of early detection of preeclampsia and antenatal surveillance in women with chronic hypertension remains controversial.[7]

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CLINICAL PERSPECTIVE

What Is New?

- The soluble fms-like tyrosine kinase 1/placental growth factor ratio has a high predictive accuracy for delivery because of maternal and fetal complications in women with suspected superimposed preeclampsia.

What Are the Clinical Implications?

- Angiogenic imbalance in women with suspected superimposed preeclampsia is associated with a significantly shorter time to delivery interval.

Nonstandard Abbreviations and Acronyms

PlGF	placental growth factor
sFlt-1	soluble fms-like tyrosine kinase 1

Angiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) are useful tools for predicting the development of preeclampsia.[8–11] The utility of angiogenic markers was shown in both singleton and twin pregnancies.[8,10] It is possible that the sFlt-1/PlGF ratio is beneficial in distinguishing pregnant women with uncontrolled chronic hypertension from those developing superimposed preeclampsia.[12,13] However, the evidence of the utility of the sFlt-1/PlGF ratio in pregnant women with chronic hypertension is scarce and conflicting.[14–16] Costa et al reported no significant differences in the sFlt-1/PlGF ratio between women with chronic hypertension and superimposed preeclampsia before 32 weeks of gestation,[15] while Perni et al reported a higher sFlt-1/PlGF ratio in early-onset superimposed preeclampsia between 20 and 28 weeks' gestation compared with women with chronic hypertension only.[16] In support of the angiogenic markers, Bramham et al suggested an association between lower PlGF levels and raised urine albumin:creatinine ratio.[17] The available literature focused on the predictive value of the sFlt-1/PlGF ratio for the development of preeclampsia in women with chronic hypertension, while data on other clinically relevant outcomes, such as delivery because of maternal and fetal indications related to superimposed preeclampsia, are missing.

Therefore, in this study, we aimed to evaluate the utility of sFlt-1, PlGF, and their ratio for predicting delivery because of superimposed preeclampsia in women with chronic hypertension.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. This was a retrospective analysis of prospectively collected data recorded in an electronic database (Viewpoint 5.6.8.428, Wessling, Germany) between January 2013 and October 2019. The study was approved by the local research ethics committee (approval number 1882/2018) of the Medical University of Vienna. No written informed consent for study participation was required. The inclusion criteria were women with singleton pregnancies and chronic hypertension with suspected superimposed preeclampsia (ie, presenting with symptoms of preeclampsia including worsening of hypertension, epigastric pain, new-onset edema, new-onset proteinuria [1+ protein in dipstick urine test], high blood pressure [≥140/90 mm Hg] despite antihypertensive treatment, dyspnea or neurological symptoms, low platelet count [<100 000 μL], and elevated liver enzymes [>2× upper reference range]). Women with superimposed preeclampsia at initial presentation, those who delivered within 1 week of assessment for reasons other than preeclampsia (spontaneous preterm, term or elective delivery, etc), chronic kidney disease, history of cardiac disease, pregnancies with aneuploidy, genetic syndromes, or major structural fetal anomalies were excluded. Women who did not deliver at the Department of Obstetrics and fetomaternal Medicine at the Medical University of Vienna were also excluded because of missing outcome data. As part of the routine assessment in women with suspected preeclampsia, a blood sample was taken by venipuncture and stored in a collection tube without anticoagulants to analyze maternal serum levels for sFlt-1, PlGF, and their ratio. The angiogenic marker concentrations were assessed in parallel by commercially available fully automated assays on Elecsys (Roche Diagnostics, Penzberg, Germany) platform. The analysis was undertaken by biomedical technicians, who were blinded to all clinical details, but the results were available to the obstetricians.

Superimposed preeclampsia was defined according to the revised criteria of the International Society for the Study of Hypertension in Pregnancy in 2014.[18] Chronic hypertension was determined as high blood pressure (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) predating pregnancy or diagnosed up until 20 weeks of gestation. In women with underlying chronic hypertension, superimposed preeclampsia was diagnosed when 1 or more of the following features of preeclampsia were present exceeding preexisting hypertension: new-onset significant proteinuria, elevated liver enzymes (transaminase levels 2× above the upper reference

range), low platelet count (<100 000/μL), severe dyspnea or neurological symptoms of preeclampsia (ie, persistent visual scotomata, altered mental status, blindness, stroke, hyperreflexia accompanied by clonus, and severe headaches accompanied by hyperreflexia or eclampsia). Significant proteinuria was diagnosed with either protein/creatinine ratio of ≥30 mg/mmol or ≥300 mg protein excretion in 24 hours. Hemolysis, elevated liver enzymes, low platelet count syndrome was defined as increased transaminases (aspartate aminotransferase and alanine aminotransferase concentrations >2× upper reference interval), reduced platelet count (<100 000/μL), plus at least 1 hemolysis criterion (increased lactate dehydrogenase concentration >2× upper reference intervals or serum indirect bilirubin concentration >1.2 mg/dL or reduced serum haptoglobin concentration <0.3 g/L). Superimposed preeclampsia was not diagnosed solely on the basis of worsening of hypertension.

The primary outcome of the study was the utility of angiogenic markers for the prediction of delivery because of maternal indications only and fetal indications primarily related to superimposed preeclampsia in women with underlying chronic hypertension. Delivery because of maternal indications was defined as women delivering because of maternal complications of preeclampsia including severe hypertension (≥170/110 mm Hg) despite 2 types of antihypertensive drugs, progressive thrombocytopenia, severe dyspnea, abnormal transaminase levels (aspartate aminotransferase and alanine aminotransferase concentrations >2× upper reference interval), or hemolysis, elevated liver enzymes, low platelet count syndrome. Delivery because of fetal indications primarily (with or without secondary features of maternal preeclampsia) was defined as women delivering because of fetal complications including placental abruption associated with fetal compromise (abnormal fetal Doppler or abnormal cardiotocography), severe fetal growth restriction or fetal compromise detected via cardiotocography or fetal Doppler. Estimated fetal weight and umbilical artery Doppler percentiles were calculated from published reference ranges.[19,20] The outcome groups were specified as follows: delivery because of maternal indications related to superimposed preeclampsia, fetal indication primarily and other reasons, including elective cesareans and inductions at term because of maternal comorbidities (chronic hypertension, diabetes mellitus, macrosomia, previous cesarean section, breech presentation, maternal request), spontaneous vaginal deliveries, and spontaneous preterm deliveries. We have also reported composite adverse outcomes for descriptive purposes. Composite adverse maternal outcome was defined as follows: maternal intensive care unit admission, maternal death, maternal lung edema, liver dysfunction, renal insufficiency, postpartum hemorrhage, and seizure, while composite adverse neonatal outcome was defined as follows: neonatal intraventricular hemorrhage, retinopathy of prematurity, respiratory distress syndrome, necrotizing enterocolitis, ventilation support, and neonatal seizures.

Even though obstetricians were not blinded to the results of the sFlt-1/PlGF ratio, there was no local protocol recommending delivery based on increased sFlt-1/PlGF ratio only at the time of the study period.

Statistical Analysis

Continuous variables were represented as median and interquartile range regardless of the distribution assumtions. Categorical variables were represented as number and percentage of total. Shapiro–Wilk test and visual inspection of quantile-quantile plots were used for verifying normality of continuous variables. Mann–Whitney *U*, independent samples *t* test, χ^2, or Fisher–Freeman–Halton tests were used for group comparison where appropriate. The accuracy of last angiogenic markers was assessed with binominal logistic regression and odds ratios (OR) with 95% CIs were calculated. Multivariable logistic regression was used to obtain adjusted ORs for angiogenic markers. Overall predictive performance was assessed with receiver operating characteristics curves. Receiver operating characteristics curves were compared using De Long's test. The predictive accuracy, sensitivity, specificity, positive and negative predictive values, and their bootstrapped CIs were calculated. Subgroup analyses for gestational age at assessment were also performed because the predictive performance of angiogenic markers is known to differ between early and late preterm periods. Time to the delivery because of maternal or fetal indications was assessed with Cox regression and hazard ratios (HRs) were estimated. Women who did not have intervention because of maternal or fetal indications of preeclampsia at the time of delivery were considered right censored. Proportional hazards assumptions were tested for each tested covariate. The level of statistical significance was considered as $P<0.05$. All analyses were performed using R for Statistical Computing Software (Version 4.0.2).

RESULTS

Characteristics and Outcomes of the Study Population

The study included 142 women with chronic hypertension evaluated because of suspected superimposed

preeclampsia. Of those, 27 women (19.0%) delivered because of maternal indications only, 17 women (12.0%) delivered because of fetal indications primarily, and 98 women (69.0%) delivered because of other reasons. Other reasons included women who delivered because of maternal indications only, had significantly higher systolic blood pressure (median: 173.0 versus 145.5 mm Hg, $P<0.001$), diastolic blood pressure (median: 104.0 versus 94.0 mm Hg, $P<0.001$), and lower body-mass index (median: 27.3 versus 32.4 kg/m^2, $P=0.021$) compared with women who delivered for other reasons (Table 1). Composite neonatal (48.1% versus 6.1%, $P<0.001$) and maternal adverse (25.9% versus 0.0%, $P<0.001$) outcomes were more common in women who delivered because of maternal indications only, compared with women delivered for other reasons. Similar findings were found in women with early-onset preeclampsia and late-onset preeclampsia versus women without preeclampsia (Table S1). Women who delivered because of fetal indications primarily were significantly younger (median maternal age 31.0 versus 34.0 years, $P=0.014$), had significantly lower gestational age at assessment (median 30.9 versus 34.7 weeks, $P=0.027$), higher diastolic blood pressure (median 106.0 versus 94.0 mm Hg, $P<0.001$), and lower body-mass index (median 26.1 versus 32.4 kg/m^2, $P=0.021$) compared with women who delivered because of other reasons. Composite neonatal outcome was significantly more common (64.7% versus 6.1%, $P<0.001$) in women who delivered because of fetal indications primarily, while there was no difference in composite maternal outcome (5.9% versus 0.0%, $P=0.319$) compared with women who delivered because of other reasons. Both women who delivered because of maternal indications and those for fetal indications had a significantly higher sFlt-1/PlGF ratio (median 99.9 and 120.2 versus 7.3, respectively, $P<0.001$ for both) and lower PlGF levels (median 73.6 and 53.3 versus 320.0 pg/mL, respectively, $P<0.001$ for both) compared with women who delivered because of other reasons.

Factors Associated With Delivery Because of Maternal or Fetal Indications

Univariable logistic regression analysis demonstrated that smoking (OR, 0.21; 95% CI, 0.05–0.66, $P=0.016$), maternal body-mass index (OR, 0.57; 95% CI, 0.34–0.90, $P=0.023$), estimated fetal weight centile (OR, 0.22; 95% CI, 0.11–0.39, $P<0.001$), umbilical artery Doppler pulsatility index percentile (OR, 2.03; 95% CI, 1.33–3.27, $P=0.016$), and gestational age at sampling (OR, 0.63; 95% CI, 0.43–0.90, $P=0.012$) were significantly associated with delivery because of either maternal or fetal indications. Both sFlt-1/PlGF ratio (OR, 3.96; 95% CI, 2.63–6.59, $P<0.001$) and PlGF levels (OR, 0.12; 95% CI, 0.05–0.23, $P<0.001$) were significantly associated with the risk of delivery because of either maternal or fetal indications. Maternal serum angiogenic markers remained significantly associated with the risk of delivery because of either maternal or fetal indications after adjusting for the effect of smoking, maternal body-mass index, estimated fetal weight centile, gestational age at assessment, and umbilical artery Doppler pulsatility index ($P<0.001$ for all, Table 2).

Predictive Accuracy and Prognostic Value of Angiogenic Markers

The predictive accuracy of angiogenic markers was assessed using receiver operating characteristics curves and area under the curve (AUC) values. Both maternal serum sFlt-1/PlGF ratio and PlGF were strong predictors for the risk of delivery because of superimposed preeclampsia, whether for maternal or fetal indications ($P<0.05$). There were no significant differences in the AUC values of sFlt-1/PlGF ratio ($P>0.10$ for all, De Long's test) for predicting delivery because of maternal or fetal indications (AUC, 0.91; 95% CI, 0.86–0.96), maternal indication only (AUC, 0.89; 95% CI, 0.81–0.96), and fetal indication primarily (AUC, 0.95; 95% CI, 0.91–0.99) (Figure 1). There were no significant differences in the AUC values of PlGF levels ($P>0.10$ for all, De Long's test) for predicting delivery because of maternal or fetal indications (AUC 0.90, 95% CI, 0.85–0.96), maternal indication only (AUC, 0.88; 95% CI, 0.81–0.96), and fetal indication primarily (AUC, 0.93; 95% CI, 0.88–0.98) (Figure 2). There were no significant differences between sFlt-1/PlGF ratio and PlGF levels for predicting any outcomes ($P>0.10$, De Long's test).

The sensitivity, specificity, and positive and negative predictive value of various cut-offs of maternal serum sFlt-1/PlGF ratio (≥85 and ≥110) and PlGF levels (<100 and <12 pg/mL) are available in Table 3. The sensitivity, specificity, and positive and negative predictive value of all cut-offs except PlGF <12 pg/mL were similar for predicting delivery because of maternal or fetal indications, maternal indication only, and fetal indication primarily with overlapping CIs (Table 3). Angiogenic markers at various cut-offs (sFlt-1/PlGF ≥85 or ≥110) were able to rule out and rule in delivery because of maternal or fetal indications with a negative predictive probability >80% and positive predictive probability >85%. A serum PlGF level <100 pg/mL had the highest negative predictive value (87.1%, 91.0%, and 95.3%) across all outcomes (delivery because of maternal or fetal, maternal only, and fetal primarily) at the expense of positive predictive value, but CIs were overlapping with those of sFlt-1/PlGF ratio.

Table 1. Characteristics of Patients Who Delivered Because of Maternal, Fetal Indications or Because of Other Reasons

Variables	Delivery Because of Maternal Indications Only* (n=27)	Delivery Because of Fetal Indications Primarily† (n=17)	Delivery for Other Reasons‡ (n=98)	*P* Value§,‖	*P* Value¶
Maternal age (y), median (IQR)	35.0 (20.0–38.0)	31.0 (26.0–33.0)	34.0 (28.2–37.0)	0.468	0.014
Gestational age at sampling (wks), median (IQR)	31.4 (27.6–34.9)	30.9 (25.1–34.1)	34.7 (30.5–36.5)	0.055	0.027
Systolic blood pressure in mm/Hg, median (IQR)	173.0 (153.0–185.0)	150.0 (142.5–166.0)	145.5 (135.0 –153.0)	<0.001	0.091
Diastolic blood pressure in mm/Hg, median (IQR)	104.0 (95.0–119.0)	106.0 (99.5–112.0)	94.0 (88.0–101.7)	0.002	<0.001
Nulliparous, n (%)	15 (55.6)	7 (41.2)	34 (34.7)	0.049	0.606
Assisted reproduction, n (%)	2 (7.4)	0 (0.0)	7 (7.1)	0.474	0.895
Smoker, n (%)	2 (7.4)	1 (5.9)	25 (25.5)	0.042	0.074
Body-mass index in kg/m^2, median (IQR)	27.3 (24.5–32.1)	26.1 (24.0–31.8)	32.4 (26.3–42.1)	0.021	0.021
sFlt-1/PlGF ratio, median (IQR)	99.9 (45.6–158.8)	120.2 (72.0–325.2)	7.3 (2.6–18.4)	<0.001	<0.001
PlGF in pg/mL, median (IQR)	73.6 (51.4–117.3)	53.3 (24.6–91.2)	320.0 (159.0–468.0)	<0.001	<0.001
Estimated fetal weight, percentile	7.1 (0.4–23.3)	3.4 (0.0–7.5)	53.0 (26.1–83.9)	<0.001	<0.001
Estimated fetal weight <10th percentile	14 (51.8)	11 (64.7)	14 (14.3)	<0.001	<0.001
Umbilical artery Doppler PI, percentile	65.1 (43.8–85.1)	96.7 (78.7–99.8)	57.6 (23.9–78.6)	0.145	<0.001
Umbilical artery Doppler PI >95th percentile	3 (11.1)	8 (47.0)	3 (3.1)	0.083	<0.001
Gestational age at delivery (wks), median (IQR)	33.9 (30.9–37.1)	31.3 (26.4–37.1)	38.5 (38.0–39.6)	<0.001	<0.001
Composite maternal outcome, n (%)#	7 (25.9)	1 (5.9)	0 (0.0)	<0.001	0.319
Maternal death	0 (0.0)	0 (0.0)	0 (0.0)	…	…
Maternal ICU admission	4 (14.8)	0 (0.0)	(0.0)	…	…
Lung edema	1 (3.7)	0 (0.0)	(0.0)	…	…
Liver dysfunction	3 (11.1)	1 (5.9)	(0.0)	…	…
Renal insufficiency	2 (7.4)	0 (0.0)	0 (0.0)	…	…
Postpartum hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	…	…
Seizures	0 (0.0)	0 (0.0)	0 (0.0)	…	…
Stillbirth or neonatal death	0 (0.0)	2 (11.8)	2 (2.0)	0.999	0.043
Apgar score <7 at 5th min	0 (0.0)	2 (11.8)	1 (1.0)	0.999	0.010
Composite neonatal outcome**	13 (48.1)	11 (64.7)	6 (6.1)	<0.001	<0.001
NICU admission	13 (48.1)	10 (58.8)	5 (5.1)	…	…
Ventilator support	13 (48.1)	10 (58.8)	4 4.1)	…	…
Necrotizing enterocolitis	0 (0.0)	0 (0.0)	0 (0.0)	…	…
Respiratory distress syndrome	13 (48.1)	9 (52.9)	3 (3.1)	…	…

(*Continued*)

Table 1. Continued

Variables	Delivery Because of Maternal Indications Only* (n=27)	Delivery Because of Fetal Indications Primarily† (n=17)	Delivery for Other Reasons‡ (n=98)	*P* Value§,‖	*P* Value¶
Intraventricular hemorrhage	0 (0.0)	1 (5.9)	0 (0.0)	…	…
Retinopathy of prematurity	0 (0.0)	5 (29.4)	0 (0.0)	…	…
Neonatal seizures	0 (0.0)	1 (5.9)	0 (0.0)	…	…

ICU indicates intensive care unit; IQR, interquartile range; NA, not applicable; NICU, neonatal intensive care unit; PlGF, placental growth factor; PI, pulsatility index; and sFlt-1, soluble fms-like tyrosine kinase-1.

*Severe hypertension (≥170/110 mm Hg) despite 2 types of antihypertensive drugs, progressive thrombocytopenia, severe dyspnea, abnormal transaminase levels (aspartate aminotransferase and alanine aminotransferase concentrations >2× upper reference interval), hemolysis, elevated liver enzymes, low platelet count syndrome.

†Placental abruption associated with fetal compromise (abnormal fetal Doppler or abnormal cardiotocography), severe fetal growth restriction or fetal compromise detected via cardiotocography or Doppler.

‡Elective cesarean, term induction, spontaneous delivery.

§Mann–Whitney *U*, χ^2, or Fisher Freeman Halton test, where appropriate.

‖Delivery because of only maternal indications with preeclampsia vs delivery because of other reasons.

¶Delivery because of fetal indications with preeclampsia vs delivery because of other reasons.

#Any of the following: maternal intensive care unit admission, maternal death, lung edema, liver dysfunction, renal insufficiency, postpartum hemorrhage, and seizure.

**Any of the following: intraventricular hemorrhage, retinopathy of prematurity, respiratory distress syndrome, necrotizing enterocolitis, ventilation support, neonatal seizures, and neonatal death.

Prognostic Value of Angiogenic Markers for Time to Delivery

Half of women with angiogenic imbalance (sFlt-1/PlGF ratio ≥85 and PlGF levels <100 pg/mL) delivered because of maternal or fetal indications within 1.6 weeks (95% CI, 1.0–2.4 weeks) (Figure 3). Only 11.1% of women without angiogenic imbalance delivered because of maternal or fetal indications within 6 weeks of assessment. Maternal serum angiogenic imbalance was strongly associated with shorter time to delivery (HR, 0.09; 95% CI, 0.04–0.17, *P*<0.001). A sensitivity analysis was performed for women below and above 32 weeks' gestation at the time of assessment (Figure S1 left and right). Angiogenic imbalance was associated with shorter time to delivery in both instances (<32 week's gestation HR: 0.05; 95% CI, 0.02–0.17, >32 weeks' gestation: HR, 0.12; 95% CI, 0.05–0.32, *P*<0.001 for both).

Table 2. Logistic Regression Analysis Showing Factors Associated With Delivery Because of Maternal and/or Fetal Indications

Variables	OR (95% CI)*	*P* Value†	aOR (95% CI)	*P* Value‡
Maternal age (y)	0.87 (0.60–1.25)	0.448	…	…
Nulliparous	1.79 (0.86–3.74)	0.120	…	…
Assisted reproduction	0.65 (0.09–2.84)	0.600	…	…
Smoker	0.21 (0.05–0.66)	0.016	…	…
Body-mass index (kg/m^2)	0.57 (0.34–0.90)	0.023	…	…
Gestational age at sampling (wks)	0.63 (0.43–0.90)	0.012	…	…
Estimated fetal weight, percentile	0.22 (0.11–0.39)	<0.001	…	…
Umbilical artery Doppler PI, percentile	2.03 (1.33–3.27)	0.001	…	…
sFlt-1/PlGF ratio	3.96 (2.63–6.59)	<0.001	4.80 (2.40–12.4)	<0.001
PlGF in pg/mL	0.12 (0.05–0.23)	<0.001	0.09 (0.02–0.28)	<0.001
sFlt-1/PlGF ratio >85	34.9 (11.9–130.2)	<0.001	9.96 (2.36–54.1)	<0.003
sFlt-1/PlGF ratio >110	29.7 (9.23–133.6)	<0.001	8.61 (1.59–74.9)	0.023
PlGF <100 pg/mL	19.0 (7.89–49.8)	<0.001	10.5 (2.96–43.1)	<0.001

Adjusted odds ratios for maternal serum angiogenic markers were obtained after adjusting for maternal smoking, body-mass index, estimated fetal weight percentile, and umbilical artery Doppler pulsatility index percentile. aOR indicates adjusted odds ratio; OR, odds ratio; PI, pulsatility index; PlGF, placental growth factor; and sFlt-1, soluble fms-like tyrosine kinase-1.

*Odds ratios correspond to 1 standard unit change in respective variables. Continuous variables were scaled using the population mean and SD.

†Univariable binomial logistic regression.

‡Multivariable binomial logistic regression.

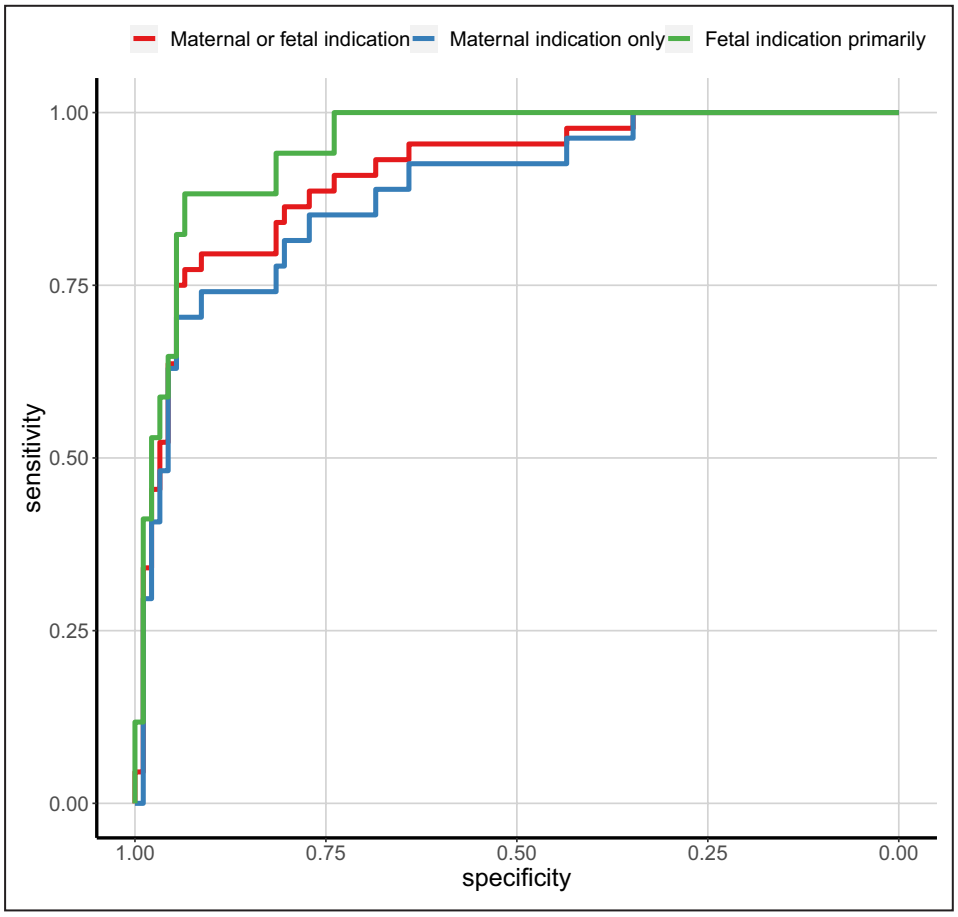

Figure 1. Receiver operating characteristics curves of maternal serum sFlt-1and PlGF for predicting delivery because of maternal or fetal indications in women with chronic hypertension and suspected preeclampsia.
There were no significant differences for area under the curve (AUC) values between maternal or fetal indication (AUC, 0.91; 95% CI, 0.86–0.96), maternal indication only (AUC, 0.89; 95% CI, 0.81–0.96), and fetal indication primarily (AUC, 0.95; 95% CI, 0.91–0.99) outcomes for sFlt-1/PlGF ratio (P>0.10 for all, De Long's test). PlGF indicates placental growth factor and sFlt-1, soluble fms-like tyrosine kinase-1.

DISCUSSION

Summary of the Study Key Findings

Maternal serum angiogenic markers were able to predict delivery because of maternal and fetal indications in women with suspected superimposed preeclampsia. The AUC values of angiogenic markers were high for both predicting delivery because of maternal indication only or fetal indications primarily. Half of women with angiogenic imbalance delivered because of maternal or fetal indications within <2 weeks of assessment.

Strengths and Weaknesses

The novel aspect of this study is the assessment of the predictive accuracy of the sFlt-1/PlGF ratio for delivery because of maternal or fetal indications related to superimposed preeclampsia in women with chronic hypertension. Furthermore, we described the prognostic value of maternal serum angiogenic markers using survival analysis, taking the assessment to delivery interval into account.

However, our study has some limitations. Clinicians were not blinded to the sFlt-1/PlGF values in women with suspected superimposed preeclampsia. Therefore, we cannot rule out the possibility of intervention bias. Nevertheless, there was no local protocol or guideline recommending delivery solely on the basis of angiogenic markers in women with chronic hypertension, diminishing the likelihood of intervention bias. We did not assess the predictive accuracy of angiogenic markers for a diagnosis of superimposed preeclampsia but instead opted for evaluation of delivery because of maternal or fetal indications related to superimposed preeclampsia as the more clinically pertinent outcome. The predictive performance of angiogenic markers can differ between development

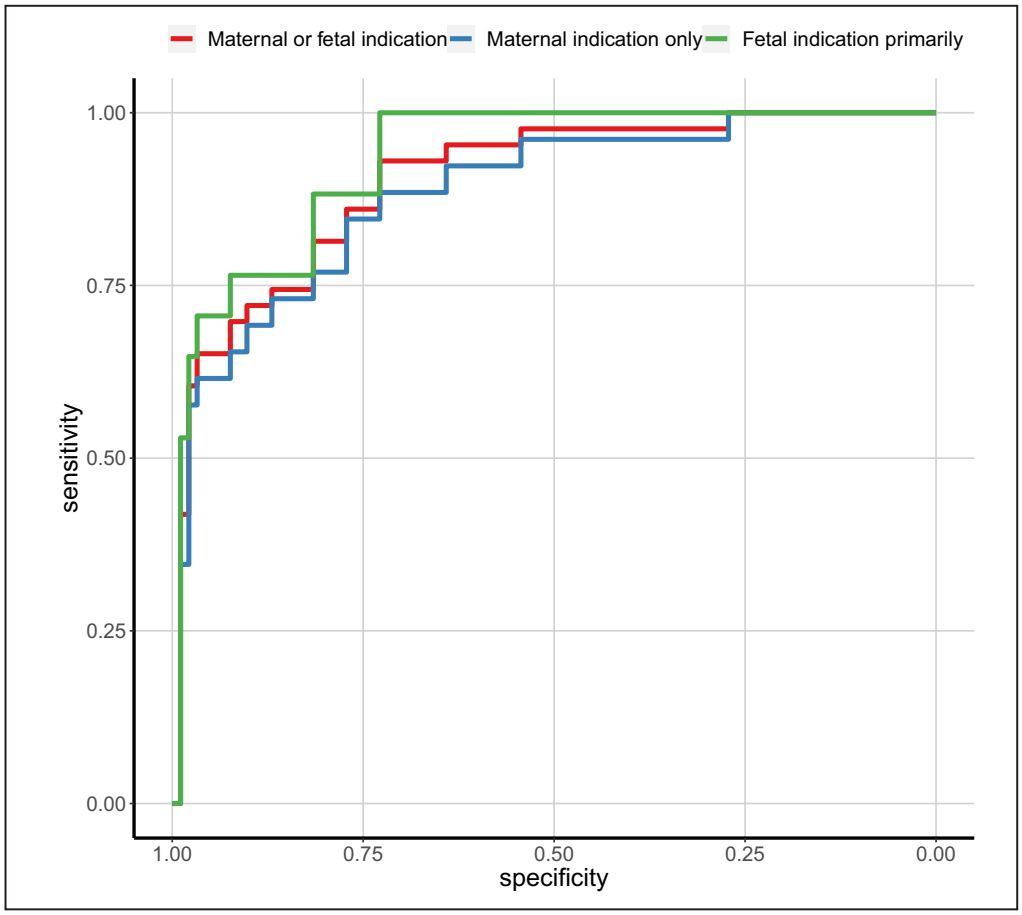

Figure 2. Receiver operating characteristics curves of maternal serum PlGF for predicting delivery because of maternal or fetal indications in women with chronic hypertension and suspected preeclampsia.
There were no significant differences for area under the curve (AUC) values between maternal or fetal indication (AUC, 0.90; 95% CI, 0.85–0.96), maternal indication only (AUC, 0.88; 95% CI, 0.81–0.96), and fetal indication (AUC, 0.93; 95% CI, 0.88–0.98) outcomes for maternal serum PlGF levels (P>0.10 for all, De Long's test). PlGF indicates placental growth factor.

of preeclampsia and requiring delivery because of complications of preeclampsia. Most preeclampsia cases are expectantly managed when diagnosed in early gestational ages and only the most severe ones require immediate delivery. It is uncertain whether angiogenic markers may or may not have better performance for predicting complications compared with diagnosis of preeclampsia. Finally, the assessment to delivery interval was not standardized in our analysis. Longer assessment to delivery time and lack of repeat measurements may have had a negative impact on the predictive performance of angiogenic markers in some cases.

Interpretation of the Study Findings and Comparison With Existing Literature

In the present study we were able to demonstrate that women who were delivered because of maternal and fetal indications related to superimposed preeclampsia had a significantly higher maternal serum sFlt-1/PlGF ratio than women who delivered because of other reasons. Furthermore, we described that women with angiogenic imbalance had a shorter time to delivery interval because of maternal and fetal indications, underscoring the clinically relevant additive potential of the ratio to predict time to delivery. These results are consistent with data reported by Verlohren et al[12] evaluating the sFlt-1/PlGF ratio in different forms of hypertensive disorders of pregnancy, including 42 women with chronic hypertension. In their cohort, the maternal serum levels of sFlt-1/PlGF ratio in both women with gestational hypertension and chronic hypertension were significantly lower compared with women presenting with preeclampsia, demonstrating that the ratio can be used to distinguish between different forms of hypertensive disorders. However, the total

Table 3. Predictive Accuracy of Maternal Serum sFlt-1/PlGF Ratio and PlGF Levels for Predicting Delivery Because of Maternal or Fetal Indications

Outcomes	sFlt-1/PlGF ratio ≥85	sFlt-1/PlGF ratio ≥110	PlGF <100 pg/mL	PlGF <12 pg/mL
Delivery because of maternal or fetal indications				
Accuracy	84.6 (77.4–90.2)	81.6 (74.1–87.7)	83.0 (75.5–88.9)	68.1 (59.6–75.9)
Sensitivity	61.4 (45.5–75.6)	50.0 (34.6–65.4)	72.1 (56.3–84.7)	2.3 (0.06–12.3)
Specificity	95.6 (59.2–98.8)	96.7 (90.8–99.3)	88.0 (79.6–93.9)	98.9 (94.1–99.9)
PPV	87.1 (71.6–94.8)	88.0 (75.0–84.5)	73.8 (61.1–83.5)	50.0 (6.02–94.0)
NPV	83.8 (78.1–88.3)	80.2 (75.0–84.5)	87.1 (80.6–91.6)	68.4 (67.3–69.5)
Delivery because of maternal indications only				
Accuracy	87.4 (80.1–92.8)	85.7 (78.1–91.4)	83.9 (76.0–90.0)	77.1 (68.5–84.3)
Sensitivity	59.3 (38.8–77.6)	48.1 (28.7–68.0)	69.2 (48.2–85.7)	0.0 (0.0–13.2)
Specificity	95.6 (89.2–98.8)	96.7 (90.8–99.3)	88.0 (79.6–93.9)	98.9 (94.1–99.9)
PPV	80.0 (59.3–91.6)	81.2 (57.1–93.4)	62.1 (47.0–75.1)	0.0
NPV	88.9 (83.5–92.7)	86.4 (81.5–90.2)	91.0 (76.0–90.0)	77.8 (77.4–78.1)
Delivery because of fetal indications primarily				
Accuracy	90.8 (83.8–95.5)	89.9 (82.7–94.9)	86.2 (78.3–92.1)	84.4 (76.2–90.6)
Sensitivity	64.7 (38.3–85.8)	52.9 (27.8–77.0)	76.5 (50.1–93.2)	5.9 (0.1–28.7)
Specificity	95.6 (89.2–98.8)	96.7 (90.8–99.3)	88.0 (79.6–93.9)	98.9 (94.1–99.9)
PPV	73.3 (49.8–88.4)	75.0 (47.5–90.9)	54.2 (39.0–68.6)	50.0 (6.2–93.8)
NPV	93.6 (88.5–96.5)	91.7 (87.0–94.9)	95.3 (89.5–97.9)	85.0 (83.4–86.5)

The tested cut-offs performed similarly for the prediction of delivery because of maternal or fetal indications, maternal indications only, and fetal indications with the exception of placental growth factor levels <12 pg/mL. Values are represented as percentage and 95% CI in parentheses. NPV indicates negative predictive value; PlGF, placental growth factor; PPV, positive predictive value; and sFlt-1, soluble fms-like tyrosine kinase.

sample size of women with chronic hypertension was relatively small (n=42). It was proposed that women with chronic hypertension might not show the same change in the sFlt-1/PlGF ratio when diagnosed with superimposed preeclampsia because of preexisting endothelial damage before pregnancy, compared with women with preeclampsia only.[21] However, Perni et al[16] concluded that women with early-onset superimposed preeclampsia showed significantly higher sFlt-1/PlGF ratios than women with late-onset superimposed preeclampsia comparable to the existing literature in women with preeclampsia without preexisting hypertension.[22,23] Our data support this finding. Women with early-onset superimposed preeclampsia demonstrated significantly higher values of the sFlt-1/PlGF ratio as well as significantly lower PlGF values compared with women presenting with late-onset superimposed preeclampsia.

Mayer-Pickel et al,[24] who also evaluated sFlt-1/PlGF ratios longitudinally in women at high risk for the development of preeclampsia, confirmed significantly higher sFlt-1/PlGF ratios in women with an adverse obstetric outcome, underscoring the predictive capacity of the ratio specifically in high-risk pregnancies. Interestingly, no effect of aspirin on sFlt-1/PlGF ratios in their cohort could be seen, which is in line with the observation that aspirin shows no effect on the development of superimposed preeclampsia in women with chronic hypertension.[25]

Clinical and Research Implications

This study indicates that the pro 110 are able to predict delivery because of maternal indications only and fetal indications primarily related to superimposed preeclampsia, with a high positive (range, 73.3%–88.0%) and negative predictive value (range, 80.2%–93.6%). Furthermore, women with maternal serum angiogenic imbalance had shorter time to delivery because of indications related to preeclampsia. Data on the assessment of the sFlt-1/PlGF ratio in pregnant women with chronic hypertension and subsequent preeclampsia in the published literature are scarce. Hence, studies evaluating this high-risk population for predicting the development of adverse maternal, fetal, as well as neonatal outcomes are highly needed, especially as preventive strategies such as the administration of aspirin do not show beneficial effects in women with chronic hypertension. Furthermore, as clinicians face the challenge of distinguishing between an exacerbating chronic hypertension and superimposed preeclampsia, we propose that angiogenic markers should be included as a prognostic and diagnostic tool in women with suspected superimposed preeclampsia because of their high positive and negative predictive value.

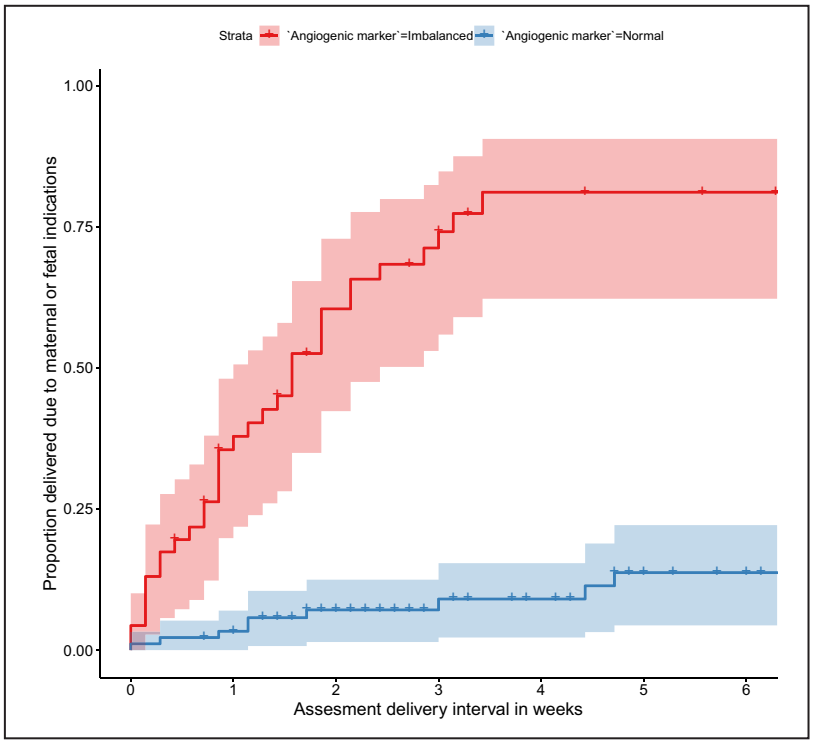

Figure 3. Survival plots showing the proportion of pregnancies delivered because of maternal or fetal indications in women with and without maternal serum angiogenic marker imbalance (red and blue lines, respectively).
Half of women with angiogenic imbalance delivered because of maternal or fetal indications within 1.6 weeks (95% CI, 1.0–2.4 weeks). Only 11.1% of women without angiogenic imbalance delivered because of maternal or fetal indications within 6 weeks. Angiogenic imbalance was defined as either sFlt-1/PlGF ratio ≥85 or PlGF levels <100. PlGF indicates placental growth factor; and sFlt-1, soluble fms-like tyrosine kinase-1.

Accordingly, several researchers questioned the logic of defining preeclampsia according to the presence of proteinuria, because angiogenic markers are superior in predicting adverse outcome compared with proteinuria.[26,27] The utility of proteinuria is further diminished in women with chronic hypertension because some women have preexisting proteinuria before pregnancy. Therefore, better strategies including angiogenic marker assessment to identify superimposed preeclampsia, as well as to predict the time to delivery, must be developed.

CONCLUSIONS

Maternal serum angiogenic markers can predict delivery because of maternal and fetal indications in women with suspected superimposed preeclampsia with high accuracy. Half of women assessed for suspected superimposed preeclampsia, showing angiogenic imbalance, were delivered because of maternal or fetal indications within 2 weeks of assessment.

ARTICLE INFORMATION

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None.

Supplementary Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of patients with early-onset preeclampsia, late-onset preeclampsia and those without preeclampsia.

Variables	Women with early-onset preeclampsia * (n=29)	Women with late-onset preeclampsia † (n=23)	*Women without preeclampsia‡ (n=90)*	*P value§ ‖*	*P value ¶*
Maternal age in years, median (IQR)	32.0 (29.0 – 37.0)	32.0 (28.0 – 37.5)	33.5 (28.2 – 37.0)	.611	.861
Gestational age at sampling in weeks, median (IQR)	27.9 (24.3 – 28.0)	35.7 (35.1-37.0)	34.4 (30.4 – 36.5)	<.001	.017
Systolic blood pressure in mm/Hg, median (IQR)	162.5 (146.2 – 184.2)	160.0 (148.2 – 176.0)	145.0 (134.0 – 150.5)	<.001	<.001
Diastolic blood pressure in mm/Hg, median (IQR)	105.5 (99.0 – 120.2)	103.0 (95.2 – 108.5)	94.0 (85.0 – 100.0)	<.001	.002
Nulliparous, n (%)	12 (41.4)	12 (52.2)	32 (35.6)	.572	.144
Assisted reproduction, n (%)	1 (3.4)	2 (8.7)	6 (6.7)	.521	.734
Smoker, n (%)	0 (0.0)	7 (30.4)	21 (23.3)	.009	.481
Body-mass index in kg/m^2, median (IQR)	28.3 (25.8 – 31.4)	26.1 (22.9 – 34.0)	30.8 (26.1 – 40.9)	.024	.026
sFlt-1/PlGF ratio, median (IQR)	162.8 (95.0 – 325.2)	63.5 (25.6 – 107.5)	6.7 (2.5 – 15.4)	<.001	<.001
PlGF in pg/mL, median (IQR)	51.2 (24.8 – 69.6)	117.0 (84.7 – 159.7)	351.4 (190.6 – 480.9)	<.001	<.001
Estimated fetal weight, percentile	2.6 (0.01 – 11.8)	7.8 (1.8 – 47.2)	53.2 (28.6 – 81.3)	<.001	.001
Estimated fetal weight <10th percentile	16 (55.2)	13 (56.5)	10 (11.1)	<.001	<.001
Umbilical artery Doppler PI, percentile	80.7 (45.3 – 98.9)	72.3 (50.4 – 84.8)	57.1 (23.6 – 78.5)	.006	.032
Umbilical artery Doppler PI > 95th percentile	8 (27.6)	3 (13.0)	3 (3.3)	<.001	.063
Gestational age at delivery in weeks, median (IQR)	29.3 (27.0 – 33.0)	37.4 (36.8 – 38.4)	38.6 (38.0 – 39.7)	<.001	.004
Composite maternal outcome, n (%) #	7 (24.1)	0 (0.0)	1 (1.1)	<.001	.999
Composite neonatal outcome, n (%) **	22 (75.9)	3 (13.0)	5 (5.6)	<.001	.211

sFlt-1: soluble fms-like tyrosine kinase-1, PlGF: placental growth factor, IQR: interquartile range, NICU: neonatal intensive care unit, NA: not applicable

* Gestational age below <34 weeks at the time of diagnosis

† Gestational age at or above 34 weeks at the time of diagnosis

‡ No diagnosis of preeclampsia at any time

§ Mann-Whitney-U, chi-squared or Fisher Freeman Halton test, where appropriate

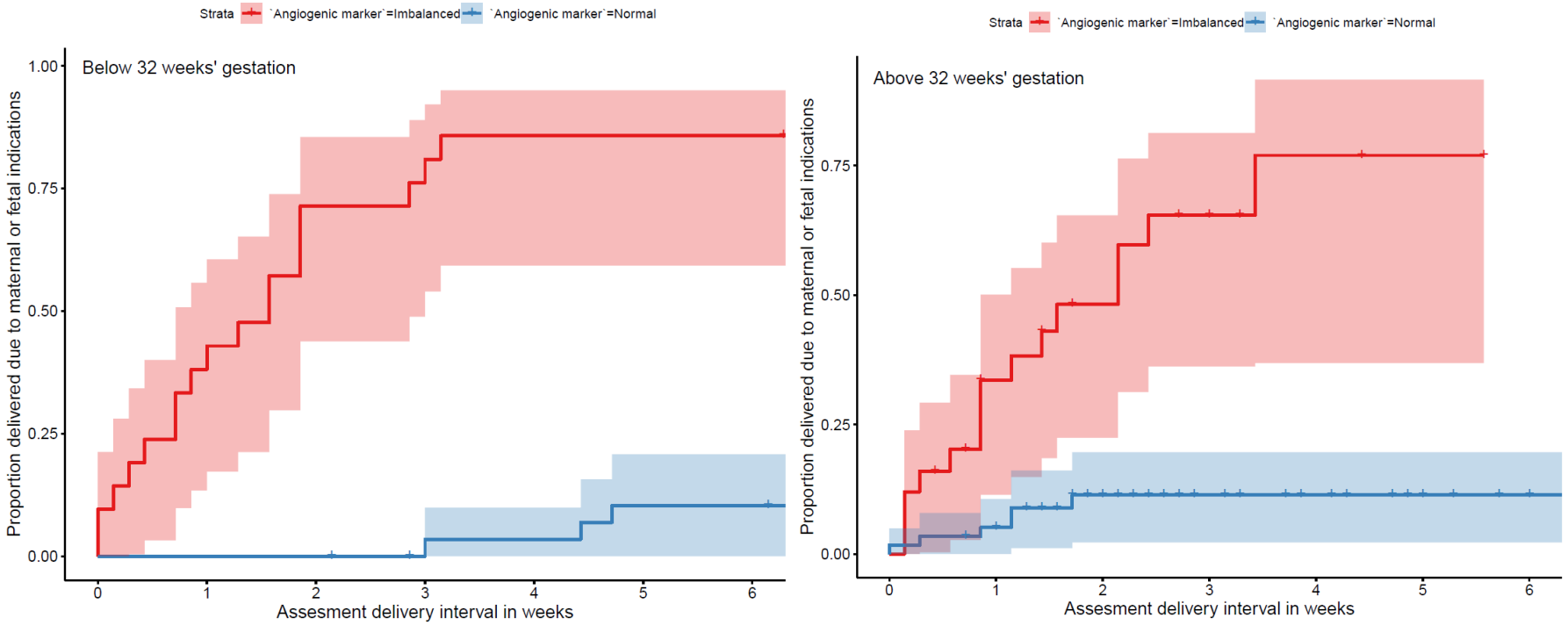
‖ Women with early-onset preeclampsia vs *Women without preeclampsia*

¶ Women with late-onset preeclampsia vs *Women without preeclampsia*

Any of the following: maternal intensive care unit admission, maternal death, lung edema, liver dysfunction, renal insufficiency, postpartum hemorrhage, seizure

** Any of the following: intraventricular hemorrhage, retinopathy of prematurity, respiratory distress syndrome, necrotizing enterocolitis, ventilation support, neonatal seizures, neonatal death

Figure S1. Survival plots showing the proportion of pregnancies delivered due to maternal or fetal indications in women with and without maternal serum angiogenic marker imbalance (red and blue lines, respectively) assessed below (left) 32 weeks' gestation and above (right).



Angiogenic imbalance was associated with shorter time to delivery in both instances (below 32 week's gestation HR: 0.05, 95% CI: 0.02 – 0.17, above 32 weeks' gestation: HR: 0.12, 95% CI: 0.05 – 0.32, P < .001 for both)