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ORIGINAL RESEARCH

Associations Between Soluble fms-Like Tyrosine Kinase-1 and Placental Growth Factor and Disease Severity Among Women With Preterm Eclampsia and Preeclampsia

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BACKGROUND: The angiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) are postulated to be pathogenic disease drivers of preeclampsia. If true, then circulating levels should become more deranged with increasing disease severity.

METHODS AND RESULTS: We investigated the association between circulating sFlt-1 and PlGF levels and severe adverse maternal outcomes among 348 women with preeclampsia. Compared with 125 women with preeclampsia without severe features, 25 women with preeclampsia and any of hemolysis, elevated liver enzymes, low platelet count syndrome, disseminated intravascular coagulation, or severe renal involvement had sFlt-1 levels that were 2.63-fold higher (95% CI, 1.81–3.82), sFlt-1/PlGF levels that were 10.07-fold higher (95% CI, 5.36–18.91) and PlGF levels that were 74% lower (adjusted fold change, 0.26 [95% CI, 0.18–0.39]). Compared with 125 women with preeclampsia without severe features, 37 with eclampsia had sFlt-1 levels that were 2-fold higher (2.02 [95% CI, 1.32–3.09]), sFlt-1/PlGF levels that were 4.71-fold higher (95% CI, 2.30–9.66) and PlGF levels that were 63% lower (0.43-fold change [95% CI, 0.27–0.68]). Compared with those without severe features, preeclampsia with severe hypertension (n=146) was also associated with altered angiogenic levels (sFlt-1, 1.71-fold change [95% CI, 1.39–2.11]; sFlt/PlGF, 2.91 [95% CI, 2.04–4.15]; PlGF, 0.59 [95%CI 0.47–0.74]). We also found that sFlt-1 and PlGF levels were altered by the number of maternal complications experienced.

CONCLUSIONS: Further angiogenic imbalance among women with preeclampsia is likely a pathogenic disease driver responsible for the life-threatening maternal complications.

Key Words: antiangiogenic factors ■ eclampsia ■ PlGF ■ preeclampsia ■ severe features ■ sFlt-1

Preeclampsia is a hypertensive disorder of pregnancy characterized by endothelial damage and injury to multiple organ systems.[1] Accumulating evidence suggests angiogenic imbalance as a central driver of disease pathogenesis, responsible for endothelial dysfunction and the maternal systemic disease. This imbalance is thought to be attributable largely to the placentally derived antiangiogenic factor–soluble fms-like tyrosine kinase-1 (sFlt-1).[2] sFlt-1 is actively secreted into the circulation, sequesters the proangiogenic

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CLINICAL PERSPECTIVE

What Is New?

- The angiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), are significantly altered among women who experience severe complications of preeclampsia, including those who experience eclampsia.
- Compared with those who had preeclampsia without severe features, women who experienced hemolysis, elevated liver enzymes, and low platelets syndrome syndrome; disseminated intravascular coagulation; or severe renal involvement had the greatest change in sFlt-1 and PlGF levels, followed by those who experienced eclampsia.

What Are the Clinical Implications?

- Our findings implicate sFlt-1 and PlGF in the pathogenesis of adverse outcomes of preeclampsia and provide further evidence to support sFlt-1 as a central driver of disease pathogenesis.
- Our findings support the premise that targeting sFlt-1 is a promising therapeutic strategy to treat the condition.

Nonstandard Abbreviations and Acronyms

HELLP syndrome	hemolysis, elevated liver enzymes, and low platelets syndrome
PI 2	Preeclampsia Intervention 2
PIE	Preeclampsia Intervention With Esomeprazole
PlGF	placental growth factor
PROVE	Preeclampsia Obstetric Adverse Effects
sFlt-1	soluble fms-like tyrosine kinase-1

molecules vascular endothelial growth factor and placental growth factor (PlGF), disrupts vascular homeostasis, and incites endothelial damage.[2] In support of the premise that sFlt-1 and PlGF may be part of the disease causal pathway, levels are altered among women with preeclampsia at diagnosis and weeks before the clinical onset of disease.[2–4]

Preeclampsia can progress to severe complications including eclampsia; pulmonary edema; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; disseminated intravascular coagulation (DIC); liver and renal impairment; stroke; coma; and death. If the angiogenic imbalance seen in preeclampsia correlates with these severe outcomes, this would add to the evidence supporting sFlt-1 as a central driver of preeclampsia. However, many of these severe maternal complications are only very rarely seen in high-income settings, where most of the research investigating angiogenic levels has occurred. Thus, the associations between sFlt-1 and PlGF and severe, life-threatening maternal complications of preeclampsia have not been fully explored.[5]

Tygerberg Hospital is a referral center servicing a population of >2 million people in Cape Town, South Africa, and has a high prevalence of preeclampsia and its complications. Thus, it represents a unique opportunity to amass a large cohort of women to investigate severe adverse outcomes of preeclampsia. Using samples collected from women with preeclampsia presenting to Tygerberg Hospital, we investigated whether altered sFlt-1 and PlGF levels were associated with severe maternal complications of preeclampsia.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Maternal plasma samples were obtained antenatally from women with preeclampsia who were prospectively recruited to three large studies at Tygerberg Hospital, Cape Town, South Africa, from 2016 to 2019. For each study, patients provided informed consent before recruitment. The first study was the PIE (Preeclampsia Intervention With Esomeprazole) trial that randomized 120 women diagnosed with preterm preeclampsia (26+0–31+6 weeks' gestation) to 40 mg esomeprazole or placebo daily[6,7] (trial registration number: PACTRPACTR201504000771349). The second study was the PI 2 (Preeclampsia Intervention 2) trial that recruited 180 women with preterm preeclampsia to 3 grams of metformin extended release or placebo daily in divided doses (trial registration number: PACTR201608001752102).[8] Both trials assessed prolongation of pregnancy following randomization and collected maternal plasma samples at randomization and twice weekly until delivery. The third study was the PROVE (Preeclampsia Obstetric Adverse Effects) study, a biobank collecting biological samples from women with preeclampsia or normotensive pregnancies.[9] Women recruited to the PROVE study were sampled at inclusion, during hospital stay, and at delivery. Women across all 3 studies with a confirmed diagnosis of preeclampsia (defined per the International Society for the Study of Hypertension in Pregnancy guidelines

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with significant proteinuria defined as ≥0.3 g/24 h on a 24-hour urine collection, a urine protein creatinine ratio ≥30 mg/mmol (0.3 mg/mg) or urine dipstick >1+ if a polymerase chain reaction was not done) who provided a blood sample during pregnancy were included in the present study, with the sample closest to delivery and after the onset of severe features assayed. Importantly, all 3 studies were undertaken in recent years at the one center and led by the same chief investigator.

Whole blood samples were collected in 9-mL EDTA tubes and centrifuged, and the resulting plasma collected and stored at −80 ˚C until assayed. Samples were shipped to the Department of Obstetrics and Gynecology, University of Melbourne, where they were assayed by research staff blinded to group allocations. All women had completed their pregnancies before biomarker assessment. Maternal plasma levels of sFlt-1 and PlGF were measured with a commercial electrochemiluminescence immunoassay platform (Roche Diagnostics).

Exposures

We divided our cohort into (1) women with preeclampsia without severe features and (2) those with preeclampsia with severe features. Women with severe features were further categorized, using adapted American College of Obstetrics & Gynecology guidelines for defining severe features[10] as (1) eclampsia; (2) pulmonary edema; (3) any of hemolysis, elevated liver enzymes, or low platelet count syndrome (defined as platelet count <100×109/L, aspartate aminotransferase >70 μ/L, and hemolysis as demonstrated by lactate dehydrogenase >600 μ/L or hemolysis on a peripheral blood smear), DIC (defined as international normalized ratio >2) or severe renal involvement (creatinine ≥120 μM/L); and (4) severe hypertension (systolic blood pressure ≥160 or diastolic blood pressure ≥110 mm Hg). Where >1 adverse outcome occurred, the hierarchy of the listed outcomes above was followed. All maternal adverse outcomes occurred antenatally.

Women were also categorized by the number of adverse outcomes experienced; 0, 1, or ≥2. In addition to the outcomes above, several women within our cohort also experienced left ventricular failure, stroke, and coma. These additional complications were also considered within analyses by number of adverse outcomes.

Finally, we assessed angiogenic levels by birth weight percentile, calculated using World Health Organization growth charts. Infants deemed <10th and <3rd birthweight percentile were compared with those born at ≥10th and ≥3rd percentiles, respectively.

Statistical Analysis

Maternal characteristics and birth outcome data were compared between women with adverse outcomes and those with preeclampsia without severe features using Fisher's exact test or chi-square test for categorical data and Kruskal-Wallis test for continuous data.

sFlt-1 and PlGF concentrations and the ratio of sFlt-1/PlGF were assessed for normality and subsequently logarithmically transformed. Angiogenic factors were analyzed using a mixed-effect linear model to account for unequal variance. Comparisons between groups were performed with a Bonferroni correction and the difference between groups presented as fold-change with 95% CIs. All analyses were performed both unadjusted and adjusted for gestational age at sampling, birth of a small for gestational age infant and original study. Statistical analysis was performed via Stata/MP V6.

Ethical approval was obtained from the Health Research Ethics Committee of Stellenbosch University (Federal Wide Assurance Number 00001372; IRB0005239; PIE M14/09/038; PI 2 M16/09/037; PROVE N17/05/048).

RESULTS

Study Population

A total of 348 women with preeclampsia were included in this study. Among these, 125 did not experience adverse maternal outcomes, while 37 had eclampsia; 15 had pulmonary edema; and 25 had any of HELLP, DIC, or severe renal involvement. The remaining 146 women experienced severe hypertension (systolic blood pressure ≥160 or diastolic blood pressure ≥110 mm Hg). Compared with women with preeclampsia without severe features, those with adverse outcomes were younger, had a lower body mass index, gave birth at earlier gestations, and had blood samples taken at a slightly earlier gestational age. Mode of birth and birth weight were not significantly different among the groups (Table 1).

Circulating Angiogenic Levels and Adverse Outcomes of Preeclampsia

Maternal plasma samples obtained closest to birth were assayed for sFlt-1 and PlGF levels. Across the total population, mean sFlt-1 and PlGF levels were 10 673.8 pg/mL (95% CI, 9618.1–11845.4) and 41.7 pg/mL (95% CI, 36.7–47.4), respectively (Figure S1, Figure S2), which resulted in a ratio of sFlt-1 to PlGF of 255.9 (95% CI, 208.8–313.6).

Given samples were obtained across 3 studies, including 2 treatment trials, we assessed the circulating angiogenic levels in the plasma samples relative to respective treatment (PIE: esomeprazole versus placebo and PI 2: metformin extended release versus placebo). Compared with women randomly assigned to the

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Table 1. Maternal Characteristics

	Preeclampsia without severe features n=125	Eclampsia n=37	Pulmonary edema n=15	Other (HELLP, DIC, renal) n=25	Severe hypertension n=146	*P* value
Age, y	28 (23–34)	21 (17–24)	28 (21–34)	25 (24–27)	30 (24–33)	<0.001
Body mass index, kg/m^2	31.1 (25.8–35. 8)	24.2 (22.7–26.8)	27.0 (22.6–31.0)	29.9 (28–33.9)	28.9 (24.0–35.2)	<0.001
Race, n (%)						
Black	83 (66.4)	23 (62.2)	9 (60.0)	10 (40.0)	93 (63.7)	0.223
Other*	41 (0.8)	14 (37.8)	6 (40.0)	15 (60.0)	53 (36.3)	
White	1 (32.8)	0	0	0	0	
Nulliparous, n (%)	46 (36.8)	29 (78.4)	5 (33.3)	9 (36.0)	47 (32.2)	<0.001
Mode of birth, n (%)						
Vaginal birth	31 (24.8)	13 (35.1)	2 (13.3)	3 (12.0)	18 (12.4)	0.002
Elective CS	26 (20.8)	2 (5.4)	1 (6.7)	5 (20.0)	17 (11.7)	
Emergency CS	68 (54.4)	22 (59.4)	12 (80)	17 (68)	110 (75.9)	
Gestation at delivery, wks	33.1 (30.1–34.1)	32.4 (30.4–36.1)	30.9 (28.9–33.7)	31.3 (29.9–31.9)	31.9 (30.1–34.0)	<0.001
Gestation at sampling, wks+d	31.8 (29.1–33.6)	32.4 (30.1–36.1)	30.9 (28.9–33.7)	30.5 (29.4–31.7)	31.2 (28.9–33.4)	0.001
Days from sampling to birth	3 (1–5)	0 (0–0)	1 (0–2)	2 (1–3.5)	2 (6–1)	0.009
Birthweight, g	1590 (1090–2100)	1750 (1200–2635)	1240 (1130–1715)	1270 (1060–1376)	1347.5 (1110–1720)	0.108
Highest systolic BP, mm Hg	150 (145–156)	167 (152–181)	167 (160–185)	168 (160–174)	166 (160–171)	<0.001
Highest diastolic BP, mm Hg	92 (85–96)	107 (99–119)	103 (99–116)	104 (98–110)	102 (100–107)	<0.001

Continuous data presented as median (interquartile range). BP indicates blood pressure; CS, cesarean section; DIC, disseminated intravascular coagulation; and HELLP, hemolysis, elevated liver enzymes, low platelet syndrome.

*Other includes those who identified as mixed race.

placebo groups, the circulating levels of angiogenic factors were not significantly altered among women randomly assigned to esomeprazole or metformin extended release (Table S1). Assessing angiogenic factor levels by gestational age at sampling, we found sFlt-1 levels increased and PlGF levels decreased with gestational age at sampling.

Investigating severe maternal complications, we found that compared with women with preeclampsia without severe features, eclampsia was associated with a significantly altered angiogenic profile, with an adjusted 2.02-fold change in sFlt-1 (95% CI, 1.32–3.09), 57% lower (0.43 [95% CI, 0.27–0.68]) PlGF and 4.71-fold (95% CI, 2.30–9.66) change in sFlt/PlGF. Conversely, compared with women with preeclampsia without severe features, those with pulmonary edema did not have a significantly different angiogenic profile (sFlt-1 1.33-fold [95% CI, 0.81–2.19]; PlGF, 0.66-fold [95% CI, 0.38–1.12]; sFlt-1/PlGF, 2.03-fold change [95% CI, 0.87–4.72]). While women experiencing any of the potentially life-threatening complications of HELLP, DIC, or severe renal involvement had significantly altered angiogenic levels, with an adjusted fold change in circulating sFlt-1 of 2.63 (95% CI, 1.81–3.82), 74% lower PlGF (0.26 [95% CI, 0.18–0.39]), and a 10.07-fold (95% CI, 5.36–18.91) higher sFlt-1/PlGF (Table 2). Compared with women with eclampsia, those women experiencing any of HELLP, DIC, or severe renal involvement had a greater change sFlt-1 levels and the ratio of sFlt-1/PlGF (*P* values=0.001 and <0.001, respectively). Severe hypertension was also associated with higher sFlt-1 (1.71-fold [95% CI, 1.39–2.11]) and sFlt-1/PlGF (2.91-fold [95% CI, 2.04–4.15]) and lower PlGF (0.59-fold [95% CI, 0.47–0.74]).

Circulating Angiogenic Levels and Number of Maternal Complications

Next, we investigated angiogenic levels by the number of severe maternal complications experienced (0, 1, ≥2). Of 348 women, 223 (64%) experienced ≥1 adverse outcome, with 67 experiencing ≥2. Altered angiogenic levels were associated with the number of complications experienced (Table 3). Compared with women without severe features, those with preeclampsia and ≥2 adverse outcomes had significantly altered levels of sFlt-1 (2.26 [95% CI, 1.67–3.07]), PlGF (0.39 [95% CI, 0.29–0.55]), and sFlt-1/PlGF (6.12 [95% CI, 3.53–10.61]). PlGF and the ratio of sFlt-1/PlGF were significantly higher among women with ≥2 adverse outcomes when compared with those with only 1 adverse outcome (*P*=0.002 and 0.028, respectively).

Antiangiogenic Levels and Birth Weight

We next investigated the association between angiogenic levels and birthing a small-for-gestational-age infant. Within our cohort, 67.8% (236/348) of women gave birth to a small-for-gestational-age infant (birth weight less than the 10th percentile according to

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Table 2. Fold Change of Maternal Antiangiogenic Levels by Severe Maternal Complication

	sFlt-1 Fold change (95% CI)			PlGF Fold change (95% CI)			sFlt-1/PlGF Fold change (95% CI)		
	Crude	Adjusted	*P* value	Crude	Adjusted	*P* value	Crude	Adjusted	*P* value
Preeclampsia, n=125	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Eclampsia, n=37	1.49 (1.06–2.09)	2.02 (1.32–3.09)	0.001	0.30 (0.20–0.46)	0.43 (0.27–0.68)	<0.001	4.91 (2.59–9.30)	4.71 (2.30–9.66)	<0.001
Pulmonary edema, n=15	1.27 (0.76–2.11)	1.33 (0.81–2.19)	0.262	0.42 (0.23–0.78)	0.66 (0.38–1.12)	0.121	3.00 (1.15–7.86)	2.03 (0.87–4.72)	0.101
HELLP, DIC, severe renal involvement, n=25	3.09 (2.08–4.56)	2.63 (1.81–3.82)	<0.001	0.19 (0.12–0.30)	0.26 (0.18–0.39)	<0.001	16.34 (7.73–34.53)	10.07 (5.36–18.91)	<0.001
Severe hypertension, n=146	1.99 (1.60–2.48)	1.71 (1.39–2.11)	<0.001	0.47 (0.36–0.61)	0.59 (0.47–0.74)	<0.001	4.22 (2.78–6.41)	2.91 (2.04–4.15)	<0.001

Women with preeclampsia without severe features (reference group) were compared with those with severe maternal complications. Adjusted analysis includes gestation at sampling, birth weight less than the third, and study from which samples were obtained from (PIE [Preeclampsia Intervention With Esomeprazole], PI 2 [Preeclampsia Intervention 2], PROVE [Preeclampsia Obstetric Adverse Effects]) as covariates. HELLP indicates hemolysis, elevated liver enzymes, low platelet syndrome; DIC, disseminated intravascular coagulation, PlGF, placental growth factor; and sFlt-1, soluble fms-like tyrosine kinase-1.

World Health Organization reference charts) and 51% (178/348) birthed an infant less than the 3rd percentile. Compared with pregnancies with a birth weight greater than the 10th percentile, birthing an infant less than the 10th percentile was associated with an adjusted fold change in sFlt-1 levels that were 2.52-fold higher (95% CI, 2.06–3.09), PlGF levels that were 68% less [95% CI, 0.25–0.41] and sFlt/PlGF ratios that were 7.94-fold higher. Similarly, angiogenic levels were significantly altered among women who birthed an infant with a birth weight less than the 3rd percentile (sFlt-1, 2.03 [95% CI, 1.67–2.45]; PlGF, 0.41 [95% CI, 0.33–0.45; sFlt/PlGF, 4.89 [95% CI, 3.44–6.96]; Table 4).

DISCUSSION

This study demonstrates that the angiogenic factors, sFlt-1 and PlGF, are significantly altered among women who experience severe complications of preeclampsia, including severe complications that are life-threatening. Compared with those who had preeclampsia without severe features, women who experienced HELLP syndrome, DIC, or severe renal involvement had the greatest change in sFlt-1 and PlGF levels, followed by those who experienced eclampsia. Angiogenic levels were not significantly altered among women who experienced pulmonary edema but were increasingly altered by the number of maternal complications experienced.

Within our study, 64% (n=223) of women with preeclampsia experienced at least 1 adverse outcome and, of these, 10% had eclampsia. This high incidence of maternal complications allowed us to investigate disease severity by the presence and type of maternal complication. Although there have been large studies investigating the utility of angiogenic markers for predicting severe complications,[11] there has been little investigation among women with established severe complications. A previous study, undertaken in Haiti, examined angiogenic levels among women with adverse outcomes, including eclampsia, and found angiogenic levels to be correlated with adverse outcomes.[5] However, this study was small, with only 35 women with preeclampsia, and the exact number of women who experienced each adverse outcome is not clear.[5] Additionally, that study compared women with adverse outcomes to normotensive women, not those with preeclampsia without severe feature.[5] Furthermore, a study by Leaños-Miranda et al[12] examined serum angiogenic levels among 689 women with hypertensive disorder, which also found the greatest change among women with HELLP and eclampsia.[12] However, within this study only 17 women developed eclampsia, and they were analyzed with those who developed HELLP syndrome.

Given that sFlt-1 is hypothesized to have a casual role in the pathogenesis of preeclampsia,[2,3,13,14] our

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findings are biologically plausible. Further placental secretion of sFlt-1 and subsequent angiogenic imbalance, may result in increased damage to the endothelium (beyond that of preeclampsia without severe features) and the onset of severe maternal complications, including HELLP syndrome, eclampsia, and severe hypertension. This hypothesis may also explain why angiogenic levels were not further perturbed among women who birthed an infant with a birth weight less than the 3rd percentile compared with less than the 10th percentile, whereby birth weight may reflect overall placental function rather than angiogenic imbalance and resulting endothelial dysfunction and the onset of severe maternal complications.

The significant implications of our findings are that our observations support quenching sFlt-1 as a therapeutic strategy to treat preeclampsia.[15,16] In fact, our work suggests that quenching its release may be able to counter the development of the most life-threatening maternal complications, such as eclampsia, HELLP syndrome, DIC, and others. It suggests that novel approaches to remove sFlt-1 from the circulation, including via apheresis or medications that reduce secretion, are plausible therapeutic strategies. However, further studies investigating these strategies are needed.

Our study has several strengths. With a large referral area, high prevalence of preeclampsia, and an established biobanking facility, recruitment from Tygerberg Hospital provided a unique opportunity to investigate rare maternal complications that have not been previously well characterized. Notably, our study included one of the largest cohorts of biological samples from women with eclampsia and pulmonary edema. Additionally, angiogenic factor levels were measured in maternal plasma via a commercial platform, which reduced the potential for interassay variability. There are some limitations to our study. First, these angiogenic factors have been previously shown to change with increasing gestation; thus, given that plasma samples were obtained across a range of gestational ages within our study, this may have implications with interpretation of our findings. To overcome this, we included gestational age at sampling as a covariate within our adjusted statistical model. The other potential limitation is that all women recruited to the PIE and PI 2 trials were delivered by 34 weeks' gestation (as per trial protocol)[7,8]; thus, it is plausible that these women may have gone on to develop additional complications without the intervention of delivery. To account for this and potential variation across studies, we also included each study as a covariate within our adjusted model. Additionally, given that an adapted version of the American College of Obstetrics & Gynecology criteria was used to categorize adverse outcomes, our findings may not be generalizable to those using standard criteria. Our study was not aimed at predicting

Table 3. Fold Change of Maternal Antiangiogenic Levels by Number of Maternal Complications Experienced

Number of severe complications	sFlt-1 Fold change (95% CI)			PlGF Fold change (95% CI)			sFlt-1/PlGF Fold change (95% CI)		
	Crude	Adjusted	*P* value	Crude	Adjusted	*P* value	Crude	Adjusted	*P* value
0 n=125	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
1 n=156	1.92 (1.54–2.39)	1.69 (1.37–2.08)	<0.001	0.46 (0.35–0.59)	0.56 (0.44–0.70)	<0.001	4.21 (2.78–6.38)	3.04 (2.12–4.34)	<0.001
≥2 n=67	1.98 (1.49–2.61)	2.26 (1.67–3.07)	<0.001	0.27 (0.20–0.38)	0.39 (0.29–0.55)	<0.001	7.19 (4.25–12.17)	5.70 (3.37–9.63)	<0.001

Women with preeclampsia without severe features (reference group) were compared with those with 1 or ≥2 severe complications. Adjusted analyses include gestation at sampling, birth weight less than the third percentile, and study from which samples were obtained from ([Preeclampsia Intervention With Esomeprazole], PI 2 [Preeclampsia Intervention 2], PROVE [Preeclampsia Obstetric Adverse Effects]) as covariates. DIC indicates disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, low platelet syndrome; PlGF, placental growth factor; and sFlt-1, soluble fms-like tyrosine kinase-1.

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Table 4. Fold Change of Maternal Antiangiogenic Levels by Birthweight Centile

	sFlt-1 Fold change (95% CI)		PlGF Fold change (95% CI)		sFlt-1/PlGF Fold change (95% CI)	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Preeclampsia, plus infant with a birth weight <10th percentile,* n=236	2.75 (2.26–3.35)	2.52 (2.06–3.09)	0.27 (0.21–0.34)	0.32 (0.25–0.41)	10.39 (7.25–14.88)	7.94 (5.49–11.48)
Preeclampsia, plus Infant with a birth weight <3rd percentile,† n=178	2.19 (1.81–2.65)	2.03 (1.67–2.45)	0.36 (0.28–0.45)	0.41 (0.33–0.52)	6.14 (4.28–8.80)	4.89 (3.44–6.96)

Adjusted analyses include gestation at sampling and study from which samples were obtained from (PIE [Preeclampsia Intervention With Esomeprazole], PI 2 [Preeclampsia Intervention 2], PROVE [Preeclampsia Obstetric Adverse Effects]) as covariates. PlGF indicates placental growth factor; and sFlt-1, soluble fms-like tyrosine kinase-1.

*Compared with those with a birth weight percentile >10th.

†Compared with those with a birth weight percentile >3rd.

severe maternal outcomes, and thus, further large prospective studies are needed to determine the utility of angiogenic factors in predicting these rare and severe maternal complications.

CONCLUSIONS

Circulating sFlt-1 and PlGF are significantly altered among women who experience severe complications of preeclampsia. Given their role in the pathophysiology of preeclampsia, the associations between sFlt-1 and PlGF levels and serious adverse maternal outcomes are biologically plausible. Our findings implicate sFlt-1 and PlGF in the pathogenesis of adverse outcomes of preeclampsia and provide further evidence to support sFlt-1 as a central driver of disease pathogenesis. Our findings support the premise that targeting sFlt-1 is a promising therapeutic strategy to treat the condition.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S2

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SUPPLEMENTAL MATERIAL

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Table S1. Fold change in circulating angiogenic levels by treatment received.

	sFlt-1 (95% confidence interval)	PlGF (95% confidence interval)	sFlt-1/PlGF (95% confidence interval)
Placebo	1 (ref)	1 (ref)	1 (ref)
Esomeprazole	1.03 (0.68, 1.57)	0.91 (0.61, 1.35)	1.14 (0.57, 2.28)
Metformin	1.10 (0.80, 1.50)	1.25 (0.84, 1.86)	0.88 (0.45, 1.71)

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Figure S1. Maternal sFlt-1 concentration across gestation

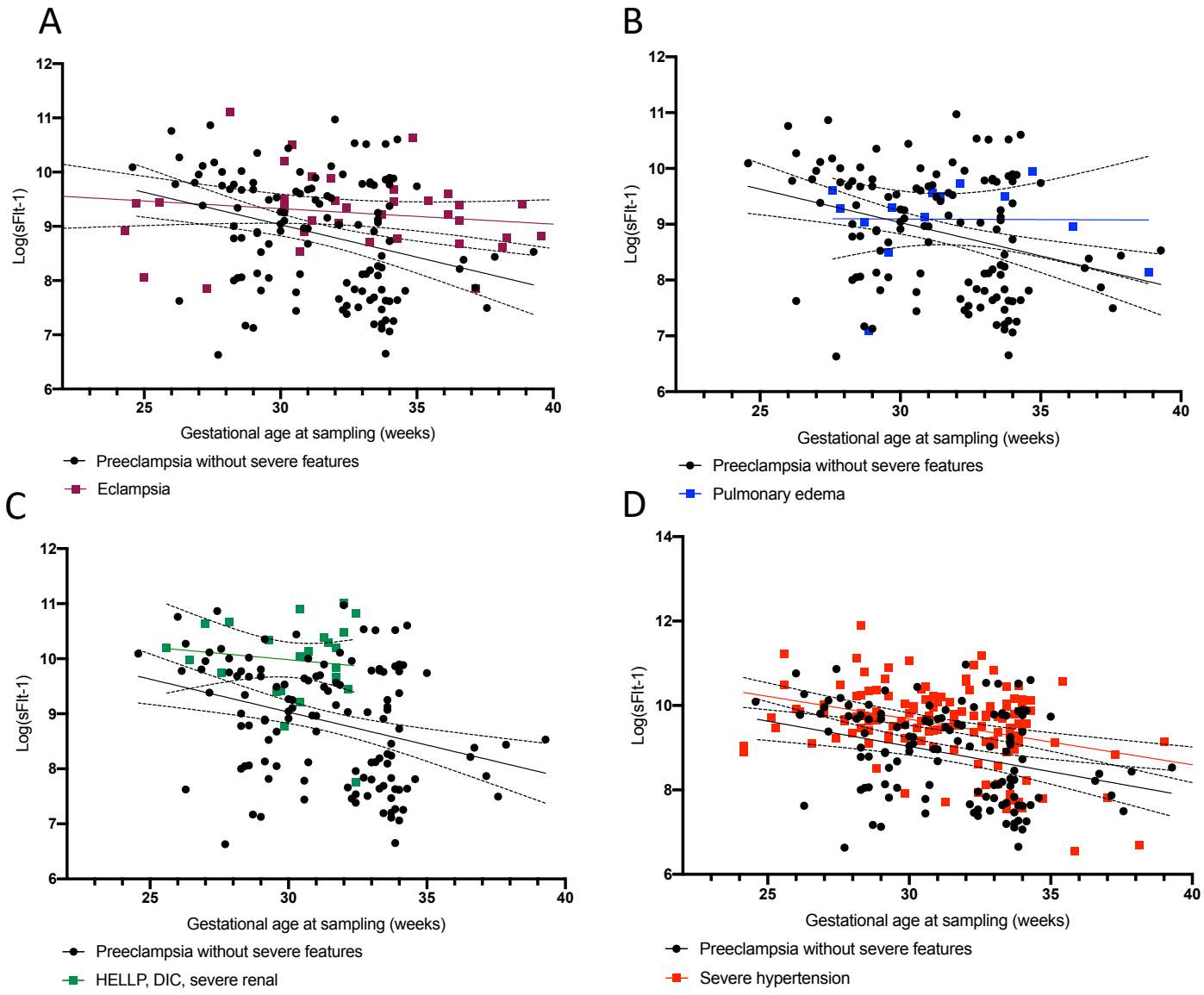

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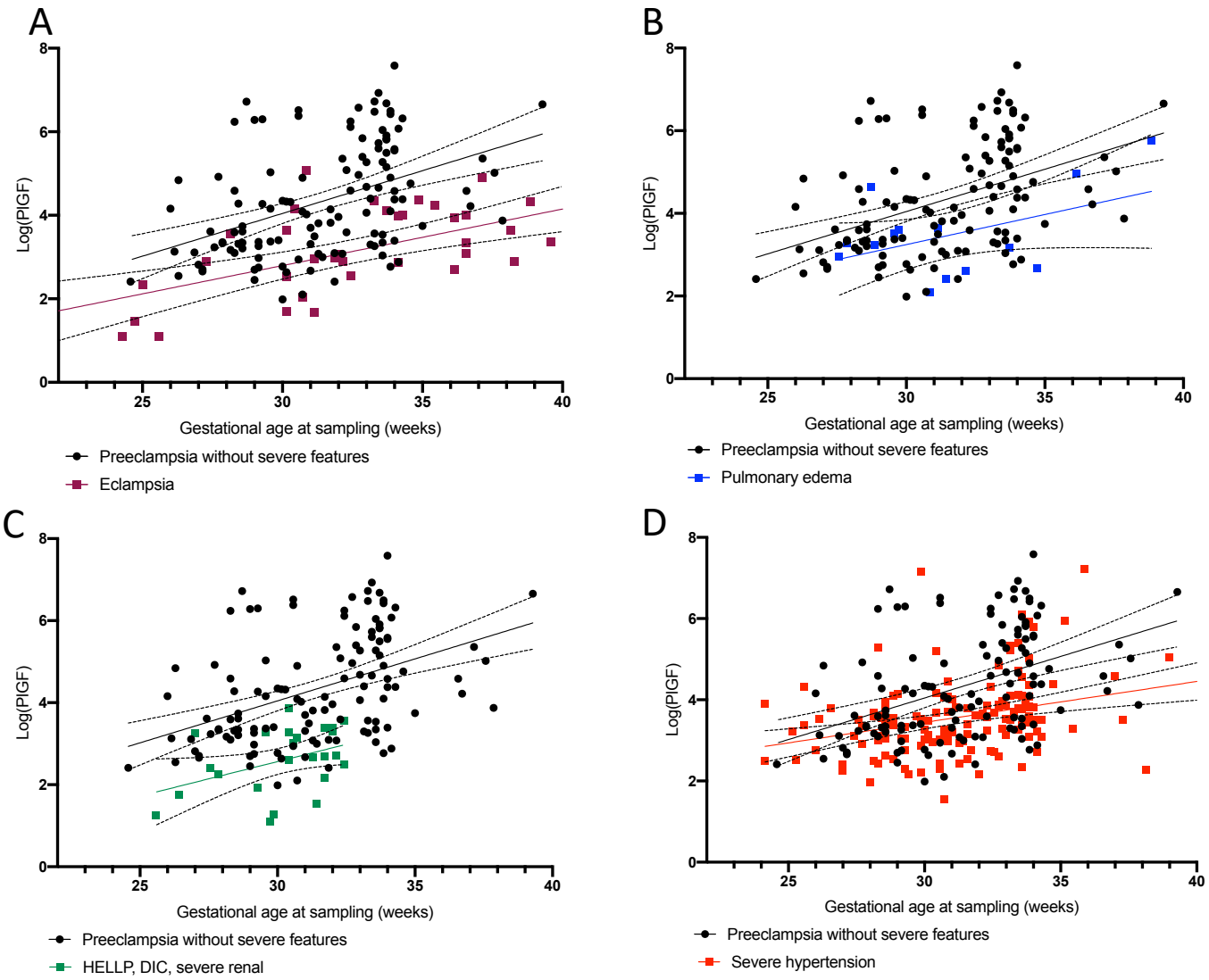
Figure S2. Maternal PlGF concentration across gestation



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