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Full Length Article

Preeclampsia biomarkers (sFlt-1/PlGF) dynamics are not disrupted by SARS-CoV-2 infection during pregnancy in a hypertensive disorder SARS-CoV-2 vaccinated cohort

Guilherme Moraes Nobrega [a,b], Luciana Pietro [a,c], Sarah Luiza Dariva [a], Isabella Ally Vasconcelos-Silva [a], Monique Possari Manari [a], Barbara Polli [d], Arthur Becker Simões [d], Julia Stucker de Almeida [d], Roberta Moschetta [d], Carolina Carvalho Ribeiro-do-Valle [a], Jose Paulo Siqueira Guida [a], Renato Teixeira Souza [a], Jose Guilherme Cecatti [a], Indira U Mysorekar [b,e], Ana Selma Picoloto [d], Maria Laura Costa [a,*]

[a] Department of Obstetrics and Gynecology, School of Medical Sciences, University of Campinas Campinas SP Brazil
[b] Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, TX 77030, USA
[c] Institute of Health Sciences, Paulista University, Campinas, SP, Brazil
[d] Department of Obstetrics and Gynecology, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil
[e] Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, USA

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ABSTRACT

Objectives: To analyze maternal and perinatal outcomes and serum levels of the preeclampsia (PE) biomarkers sFlt-1 and PlGF in pregnant women with hypertensive disorders vaccinated against SARS-CoV-2, with or without confirmed COVID-19 during pregnancy.
Methods: Multicenter (two-center) prospective cohort study secondary analysis. The cohort comprised pregnant women with hypertensive disorders who received SARS-CoV-2 vaccination, assessed from August 2021 to December 2022. Key variables included sociodemographic information, clinical background, maternal and perinatal outcomes, and biomarkers serum concentrations. A sFlt-1/PlGF ratio $\geq$ 38 was the threshold for predicting PE. The study compared outcomes based on the timing of SARS-CoV-2 infection and PE clinical onset.
Results: For biomarker analysis, 170 women provided serum samples: 31 had a confirmed COVID-19 during pregnancy, while 139 did not. Among these 170 women, 86 had chronic hypertension, and 100 developed PE. There were no significant differences in sociodemographic characteristics and gestational outcomes between the groups. The dynamics of the sFlt-1/PlGF ratio were similar regardless of COVID-19. Cesarean delivery was the most common delivery method in both groups, and there was a high rate of preterm births. No neonatal or maternal deaths were recorded.
Conclusions: The study suggests that pregnant women with hypertensive disorders who have been vaccinated against SARS-CoV-2 and subsequently infected show comparable maternal and perinatal outcomes and PE biomarker levels to those who were not infected. These results suggest that SARS-CoV-2 vaccination is protective for pregnant women, potentially reducing the association with a *PE-like* syndrome in severe cases of COVID-19 among those who are unvaccinated.

1. Introduction

Hypertensive disorders during pregnancy are significant contributors to maternal mortality and morbidity globally, with preeclampsia (PE) being one of the main condition – affecting 3 % to 6.5 % of pregnancies worldwide [1–3]. This situation has been further complicated by the COVID-19 pandemic [4–6]. As pregnant individuals are at higher risk for severe SARS-CoV-2 infection compounded by pre-existing

* Corresponding author.
E-mail address: mlaura@unicamp.br (M.L. Costa).

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conditions such as chronic hypertension, COVID-19 has led to heightened maternal and perinatal morbidity and mortality compared to the general population [7,8].

Associations between COVID-19 and PE have been identified in unvaccinated women, showing increased occurrence of PE among COVID-19 cases and higher maternal and perinatal related-morbidity [9–11]. These reports suggest an increased risk for PE in pregnant women diagnosed with COVID-19 [12]. A cohort study demonstrated that most unvaccinated pregnant women who developed severe pneumonia due to SARS-CoV-2 also exhibited PE features, unfolding a *PE-like* syndrome induced by severe COVID-19 [13]. This association is grounded on the similar pathophysiology and clinical presentation of PE and COVID-19, underscoring the unique interplay of SARS-CoV-2 during pregnancy [14–18].

PE is characterized by multisystemic organ involvement, inflammation, and endothelial damage, with eclampsia and HELLP syndrome as its most severe forms. Key biomarkers like soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) are used as predictors, with increased sFlt-1 and decreased PlGF correlating with disease onset [19–21]. The sFlt-1/PlGF ratio up to 38 cutoff can provide reassurance for the absence of PE at that given time, as well as it indicates that the development within the following week is very unlikely; staring a potential prediction value for clinical interpretation and management [22]. COVID-19 presents similar challenges for reassuring prognosis, because it is associated with multi-organ involvement and extensive inflammation, making differential diagnosis difficult, especially in SARS-CoV-2 unvaccinated severe cases where a *PE-like* syndrome can occur [13,23]. Therefore, alongside a similar clinical presentation in severe cases, SARS-CoV-2 infection, like PE, can disrupt placental biomarker balance and alter renin-angiotensin system homeostasis [18,24]. However, the sFlt-1/PlGF ratio has proven effective in distinguishing true PE cases within COVID-19-positive SARS-CoV-2 unvaccinated pregnant cohorts, highlighting the importance of these biomarkers in managing pregnancy complications [12,25]. Hence, accurate diagnosis of PE, with consideration of biomarkers, is pivotal for clinical intervention, particularly in cases potentially leading to preterm births. Timely delivery decisions significantly influence perinatal outcomes, highlighting the utility of PE biomarkers in guiding management, particularly in COVID-19 cases [25,26].

With the robust intervention of SARS-CoV-2 vaccination among pregnant and postpartum women, the clinical severity of COVID-19 has decreased, reducing severe cases and maternal deaths as vaccination rates increase [27–30]. Concomitantly, the establishment of new viral variants with more robust ecological fitness but with lower virulence characteristics replaced previously established SARS-CoV-2 Variants of Concern (VOCs), alleviating some of the burden associated with the disease [31,32]. Observing the evolving landscape of COVID-19 within SARS-CoV-2 vaccination and its implications for high-risk pregnancies with hypertensive disorders, it is key to expand the understanding of the consequences of COVID-19 and the extend evaluation on the association of COVID-19 and PE [18]. Thus, this study aimed to assess maternal and perinatal outcomes and PE biomarkers sFlt-1 and PlGF serum levels and temporal dynamics in pregnant women with hypertensive disorders after implementing vaccination against COVID-19, comparing cases with and without a history of confirmed SARS-CoV-2 infection during pregnancy.

2. Methods

2.1. Participants

The present research is a multicentric (02 institutions) secondary analysis of a prospective cohort protocol conducted within the Brazilian Network of COVID-19 in Obstetrics (REBRACO) Study group – a multicenter group of 09 Brazilian referral centers from different regions across the country – with the University of Campinas (Unicamp) as coordinating center and the Federal University of Rio Grande do Sul (UFRGS) as one of the participating centers [33,34]. In August 2021, the REBRACO Study group established a protocol for prospectively assessing the burden of disease on maternal and perinatal outcomes related to COVID-19 infection exposure during pregnancy including all the pregnant and postpartum women that consented to participate in the study protocol. The pregnant women that compose the cohort were included in different moments during pregnancy (1st, 2nd, or 3rd trimester) as well during immediate postpartum. The participants had a follow-up from the inclusion moment until the 45-day postpartum hospital visit, with a comprehensive clinical data. The participants were included from August 2021 to December 2022. The predominant circulating SARS-CoV-2 variants were Delta (from the start of participant inclusion to December/2021) and mainly Omicron (from January/2022 to the end of the follow-up). The clinical data collection and management for this paper was performed using the OpenClinica® open-source software, version 3.1. All women included on the study protocol had at least one peripheral blood sample collected at the inclusion moment, and maximum 03 blood samples collected in different time points (suggested at the 28 gestational-weeks antenatal care visit and childbirth). Within this cohort, the SARS-CoV-2 vaccinated (CoronaVac®, COMIRNATY® [Pfizer-BionTech], Janssen® and/or Oxford-AstraZeneca® COVID-19 vaccines) pregnant and postpartum women with hypertensive disorders during pregnancy were assessed. Cases without maternal blood sample collected after 20 gestational weeks or lost study protocol follow-up were excluded, considering the PE clinical diagnosis occurs after such gestational age. Clinical background and maternal and perinatal outcomes of the included cases were analyzed. The cases were grouped by clinical PE diagnosis, COVID-19 confirmed positivity during pregnancy, and biomarkers. Experimental pharmacological or immunobiological methods were not administered to any study participants.

2.2. Peripheral blood serum samples

Blood serum samples were collected from maternal peripheral blood using dry vacuum tubes with clot separator gel. To ensure sample integrity, peripheral blood samples were processed within one hour of collection. The blood tubes were centrifuged at room temperature (18 °C) for 10 min at 1200xG. Post-centrifugation, the serum was aliquoted into sterile cryotubes, with approximately 600 μl (μL) per cryotube. These cryotubes were then immediately stored in an ultrafreezer at −80 °C. The date of sample collection was recorded for analysis and calculations related to maternal outcomes, including the clinical diagnosis of PE and COVID-19 during pregnancy.

2.3. sFlt-1 and PlGF serum levels

The levels of angiogenesis-related factors sFlt-1 and PlGF in serum samples were measured using the Roche Cobas e411 analyzer (ROCHE®) with automated Elecsys® sFlt-1/PlGF kits (ROCHE®). Elecsys® sFlt-1/PlGF kits are quantitative assay for determination of biomarkers concentration by electrochemiluminescence based, requiring 50 μL of maternal serum. The protocol was executed following the manufacturer's instructions. The concentrations obtained from the assay were expressed in picograms per milliliter (pg/mL) of serum. These values were also used to calculate the sFlt-1/PlGF ratio, with a cutoff value of 38 utilized for grouping and analysis (sFlt-1/PlGF $\geq$ 38).

2.4. Clinical data

Medical charts and study interviews were reviewed to retrieve information on sociodemographic characteristics, obstetric and clinical background, and maternal and perinatal outcomes. For sociodemographic characteristics were included age (completed years at study admission) and self-referred skin color (white/non-white). In Brazil, the Brazilian Institute of Geography and Statistics (IBGE) classify the

Brazilian population based on skin color self-referred as white, black, *pardo* (brown or mixed brown), East Asian, or South American indigenous; and due to the particularly complex miscegenation in Brazil and demographic issues, the self-referred skin color variable was categorized as white or non-white for this study [35]. For obstetric and clinical background were analyzed parity (nulliparous/multiparous), singleton/twin pregnancy, chronic hypertension, gestational hypertension, diabetes, and obesity – Body Mass Index (BMI) > 30. For maternal outcomes the variables included were PE clinical diagnosis; date of diagnosis and gestational age at diagnosis), confirmed COVID-19 diagnosis (yes/ no, date of and gestational age at diagnosis), sFlt-1/PlGF ≥ 38, eclampsia, HELLP syndrome, systolic blood pressure (BP) (mmHg), diastolic blood pressure, oxygen saturation (%), route of delivery (vaginal or c-section), and maternal intensive care unit (ICU) admission. And the perinatal outcomes included were preterm birth (<37 gestational weeks; iatrogenic/spontaneous), 5th minute APGAR score < 7, neonatal ICU admission, small for gestational age (SGA), intrauterine fetal growth restriction (IUGR), abortion, stillbirth, neonatal death, and perinatal death. For confirmed COVID-19 cases during pregnancy, data on gestational age and date at diagnosis. For cases [with PE clinical diagnosis, COVID-19 positive during pregnancy and sFlt-1/PlGF ≥ 38] and cases [without PE clinical diagnosis and sFlt-1/PlGF ≥ 38], detailed information on severe features and descriptive maternal and perinatal adverse outcomes were also retrieved.

COVID-19 confirmed during pregnancy categorization considered laboratorial diagnosis based on SARS-CoV-2 viral genome (RT-qPCR) and/or viral proteins (nucleocapsid/spike based rapid chromatography tests).

Chronic hypertension was considered as high blood pressure that is present before pregnancy or is recognized before 20 weeks of gestation [36]. Gestational hypertension is hypertension arising de novo after 20 weeks gestation in the absence of proteinuria and without biochemical or hematological abnormalities [36]. And PE clinical diagnosis was considered based on the presence of hypertension associated with proteinuria (proteinuria/creatinine > 0.3 or 24 h proteinuria over 300 mg) after 20 gestational weeks, in a previously normotensive pregnant woman. PE was also considered in the absence of proteinuria if there was target organ damage [37,38].

Women with preexisting chronic hypertension were managed according to local obstetric care protocols, at the institutioń s high-risk antenatal care outpatient clinic, which included: blood pressure control (antihypertensive therapy such as methyldopa and nifedipine as first-line treatment), preventive interventions with aspirin and calcium, besides fetal surveillance for growth and vitality assessment. Additionally, for those suspected superimposed PE, hospital admission was proposed, for laboratory and clinical evaluation, with the use of magnesium sulfate for seizure prophylaxis when indicated.

2.5. Biomarkers temporal dynamics assessment and data analysis

The biomarkers temporal dynamics were analyzed performing a dispersion of sFlt-1 levels (pg/mL), PlGF (pg/mL) levels, and sFlt-1/PlGF ratio regarding the difference between serum sample collection date and date of clinical diagnosis of PE in days (Δ Preeclampsia) and COVID-19 positivity (+/-) during pregnancy. This approach was implemented to enhance the interpretation of biomarkers in serum sample collection, initially proposed in set date-points for COVID-19 exposure assessment, and not at PE clinical diagnosis. Thus, biomarker levels for individuals with one or more samples were normalized by the temporal differences between sample collection dates and clinical events (PE clinical diagnosis and COVID-19 diagnosis). Dispersions' data graphs were analyzed by linear correlations with 95 % confidence interval (CI). Correlations of biomarkers dispersion and Δ Preeclampsia were assessed by nonparametric Spearmen correlation (*r*) with two-tailed *p-value*. COVID-19 (+/-) linear correlations were tested for whether slopes and elevations are significantly different (*p-value* ≤ 0.05).

For COVID-19 positive cases with PE clinical diagnosis, a linear correlation model with 3 variables was stablished evaluating sFlt-1/PlGF ratio as the dependent variable and Δ Preeclampsia and the difference between serum sample collection date and date of COVID-19 diagnosis in days (Δ COVID-19) as the independent variables. The linear correlation model was plotted as a surface in a 3D scatter plot. Model fitness *p-value* ≤ 0.05 was considered significant.

Sociodemographic characteristics, clinical background, and maternal and perinatal outcomes were compared among groups considering biomarkers levels (sFlt-1/PlGF ≥ 38 and sFlt-1/PlGF < 38); PE clinical diagnosis and COVID-19 diagnosis during pregnancy.

Comparisons between groups were performed using conventional Chi-square test or Fishers exact (expected results less than 5) for categorical variables; and Mann-Whitney test (*U* test) for continuous variables. Outliers were considered by the ROUT method with Q = 0.2 %. Kolmogorov-Smirnov test was used to compare the cumulative frequency distributions of the Interval between the time of blood collection and diagnosis of PE (days). Categorical group analysis was performed in EPInfo 7.2.4 (CDC, United States). Dispersions linear correlations and continuous group statistical analysis tests were performed using GraphPad Prism version 7 for Mac (GraphPad Software, San Diego, CA, United States). Multivariable linear correlations model, and 3D surface model and scatter plot were performed using R software v4.1.1 with plotly package. For all analysis, p-value ≤ 0.05 was considered significant.

2.6. Ethical considerations

The research project followed all recommended rules for the use of human biological samples, with approval by the Research Ethics Committee of the University of Campinas, IRB Approval #45476421.9.1001.5404. All women signed an informed consent form authorizing the collection, storage, and use of clinical samples and data.

3. Results

A total of 1163 cases of pregnant and postpartum women were screened at antenatal care and childbirth at Unicamp and UFRGS maternity hospitals from August 2021 to December 2022, and 942 consented to participate. Of the total number of participants, 255 pregnant and postpartum women were vaccinated against SARS-CoV-2 and presented hypertensive disorder during pregnancy. Of those, 170 women were eligible for the analysis – 139 COVID-19 negative (−) cases during pregnancy (217 serum samples) and 31 COVID-19 confirmed positive (+) cases during pregnancy (44 serum samples) (Fig. 1).

When grouping women according to SARS-CoV-2 infection status during pregnancy, there were no significant difference on the sociodemographic and clinical characteristics, and maternal and perinatal outcomes analyzed between the COVID-19 (+) (n = 139) and COVID-19 (−) (n = 31) cases (Supplemental Table 1). A high incidence of PE clinically diagnosed was observed among these hypertensive disorders related pregnancies regardless COVID-19 status: 79 (56.83 %) in COVID-19 (−) and 21 (67.74 %) in COVID-19 (+) cases (*p-value* = 0.2645).

When grouping regarding PE clinical diagnosis with and without SARS-CoV-2 confirmed infection during pregnancies – COVID-19 (−)/PE (+) (n = 79) vs COVID-19 (+)/PE (+) (n = 21) – both groups presented similar clinical characteristics and outcomes (Table 1). On cases with PE clinical diagnosis, COVID-19 (−) and (+) cases during pregnancy had similar maternal age (30.95 and 31.71 age means in years, respectively, *p-value* = 0.7445), most of them were multiparous (68.35 % and 76.19 %, *p-value* = 0.4861), and higher rates of concomitant comorbidities: chronic hypertension (39.24 % and 52.38 %, *p-value* = 0.2782), diabetes (41.77 % and 42.86 %, *p-value* = 0.9287), obesity (59.49 % and 66.67 %, *p-value* = 0.5492), and gestational hypertension (6.33 % and 4.76 %, p-value = 1.0000). PE with severe features were presented in 5 participants of COVID-19 negative cases [0

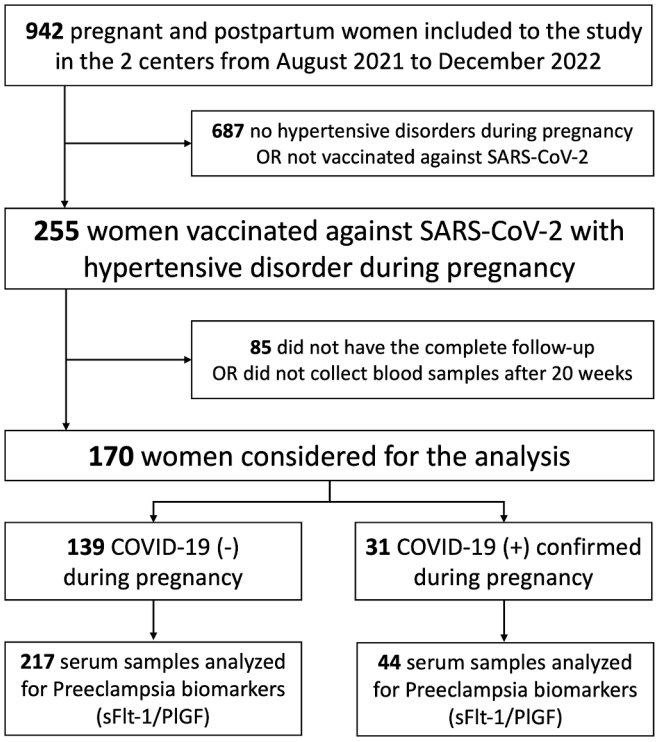

Fig. 1. Flowchart of the study included cases.

Eclampsia, 5 HELLP syndrome (6.33 %)] and in 3 participants [1 Eclampsia (4.76 %), 2 HELLP syndrome (9.52 %)] in COVID-19 positive cases (Eclampsia *p-value* = 0.2100, HELLP syndrome *p-value* = 0.6353). The cases presented high frequency of C-section (84.81 % COVID-19 negative, 90.48 % COVID-19 positive, *p-value* = 0.7280), and most of the cases had a favorable perinatal outcome – 5th minute Apgar score < 7 in 2 newborns of COVID-19 (−) pregnancies (2.53 %) and in 1 newborn (4.76 %) of COVID-19 (+) pregnancies (*p-value* = 0.5110). There was a high neonatal ICU admission in both groups (51.90 % and 47.62 %, *p-value* = 0.7273). The COVID-19 (−)/PE(+) group had higher rate of SGA than then COVID-19 (+)/PE(+) group (41.77 % and 14.29 %, ***p-value* = 0.0220).**

Participants with PE, COVID-19 (+) and sFlt-1/PlGF ≥ 38 (n = 9) were further evaluated in detail for each case (Supplemental Table 2). This description displays that half were preterm (5, 55.56 %) and all cases evolved to C-section delivery. One severe preterm case (A.9) – 26 weeks – presented fetal distress, and an extreme abnormal sFlt-1/PlGF ratio of 1,681.25.

Regarding PE biomarkers (sFlt-1/PlGF), all considered cases were grouped as sFlt-1/PlGF ≥ 38 (n = 60) or < 38 (n = 110) (Table 2). Considering cases with clinical diagnosis of PE there was significantly higher frequency in the sFlt-1/PlGF ≥ 38 (43, 71.67 %) compared to < 38 cases (57, 51.82 %) (***p-value* = 0.0120**), For COVID-19 diagnosis, the frequency was similar in both groups (*p-value* = 0.6957). In cases of sFlt-1/PlGF ≥ 38, significantly higher incidence of nulliparity (21, 35.00 %, ***p-value* = 0.0143**), higher systolic BP (mmHg) at PE diagnosis [156.33 ± (17.96), ***p-value* = 0.0354**] and preterm birth rates (33, 55.00 %, ***p-value* = 0.0190**) were observed in comparison with sFlt-1/PlGF < 38 [nulliparity: 20, 18.18 %; systolic BP (mmHg) at PE diagnosis: 150.59 ± (14.13); preterm birth: 40, 36.36 %]. Significantly higher rates of neonatal ICU admission (37, 61.66 %, ***p-value* < 0.0001**), SGA (28, 46.66 %, ***p-value* = 0.0001**) and IUGR (11, 18.33 %, ***p-value* = 0.0033**) were on cases of sFlt-1/PlGF ≥ 38 comparing and mostly due to high preterm incidence. Interval between the time of blood collection and diagnosis of PE were significantly more distant and scattered in sFlt-1/PlGF < 38 cases [–23.28 mean, (–32.93 ~ -13.63) 95 % CI] compared with sFlt-1/PlGF ≥ 38 ones [3.44 mean, (−2.94 ~ 9.82) 95 % CI], that had blood collections were closer to PE clinical diagnosis (***p-value* = 0.0005**). Cases without PE diagnosis and increases biomarker ratio were further evaluated in detail in Table 3 (n = 17). Among those 17 cases, 14 (82.35 %) presented chronic hypertension as a comorbidity. There were higher as well other comorbidities incidence, including obesity (76.47 %) and diabetes (82.35 %). Only 4 cases were related with COVID-19 confirmed during pregnancy (23.53 %). In this secondary analysis, no cases presented maternal ICU admission, abortion, stillbirth, neonatal death, or perinatal death.

Considering sFlt-1, PlGF and sFlt-1/PlGF ratio levels temporal dispersion dynamics of PE clinical diagnosed cases regarding Δ Pre-eclampsia in COVID-19 (+) (n cases = 21, n samples = 30) and COVID-19 (−) (n cases = 79, n samples = 112) cases during pregnancy, there were no overall difference within the groups (Fig. 2). sFlt-1 levels did not correlate within time in COVID-19 (−) (*r* = 01454, *p-value* = 0.1895) and COVID-19 (+) cases (*r* = -0.2081, *p-value* = 0.2845), and both linear correlations have similar slopes (*p-value* = 0.4591) and elevations (*p-*

Table 1
Clinical, obstetric characteristics and maternal and perinatal outcomes of pre-eclampsia cases comparing COVID-19 (+) confirmed during pregnancy and COVID-19 negative (−) cases.

	COVID-19 (+) during pregnancy with Preeclampsia (+)	**COVID-19 (−) during pregnancy with Preeclampsia (+)**	***p-value***
N	21	79	
Maternal age (years) ± (SD)	31.71 ± (7.17)	30.95 ± (6.67)	0.7445*
Skin color			
White	11 (52.38 %)	52 (65.82 %)	0.2568
Non-white	10 (47.62 %)	27 (34.18 %)	
Singleton pregnancy	20 (95.24 %)	73 (92.41 %)	1.0000**
Parity			
Nulliparous	5 (23.81 %)	25 (31.65 %)	0.4861
Multiparous	16 (76.19 %)	54 (68.35 %)	
Chronic hypertension	11 (52.38 %)	31 (39.24 %)	0.2782
Gestational hypertension	1 (4.76 %)	5 (6.33 %)	1.0000**
Diabetes	9 (42.86 %)	33 (41.77 %)	0.9287
Obesity (BMI > 30)	14 (66.67 %)	47 (59.49 %)	0.5492
sFlt-1/PlGF ≥ 38	9 (42.86 %)	35 (44.30 %)	0.9055
Interval between the time of blood collection and diagnosis of preeclampsia (days) (95 % CI)	−13.81 (−28.33 ~ 0.70)	−11.25 ± (−18.82—3.68)	0.9922***
Systolic BP (mmHg) ± (SD) †	149.90 ± (14.24)	153.79 ± (16.43)	0.3293*
Diastolic BP (mmHg) ± (SD) †	95.30 ± (8.34)	94.25 ± (10.77)	0.6692*
Oxygen Saturation (%) ± (SD) †	96.90 ± (1.97)	95.58 ± (8.13)	0.7535*
Eclampsia	1 (4.76 %)	0	0.2100**
HELLP syndrome	2 (9.52 %)	5 (06.33 %)	0.6353**
Preterm Birth (< 37 weeks)	11 (47.62 %)	47 (59.49 %)	0.5572
	n = 11	n = 47	
Iatrogenic	10 (90.91 %)	41 (87.23 %)	1.0000**
Spontaneous	1 (9.09 %)	6 (12.77 %)	
	n = 21	n = 79	
Delivery Route			
C-section	19 (90.48 %)	67 (84.81 %)	0.7280**
Vaginal	2 (9.52 %)	12 (15.19 %)	
5th minute APGAR score < 7	1 (04.76 %)	2 (02.53 %)	0.5110**
Neonatal ICU admission	10 (47.62 %)	41 (51.90 %)	0.7273
SGA	3 (14.29 %)	33 (41.77 %)	**0.0220****
IUGR	3 (14.29 %)	11 (13.92 %)	1.0000**

*Mann-Whitney test; **Fisher Exact; ***Kolmogorov-Smirnov; †At PE diagnosis

Table 2
Clinical, obstetric characteristics and maternal and perinatal outcomes comparing cases of sFlt-1/PlGF ≥ 38 (increased ratio) and sFlt-1/PlGF < 38.

	sFlt-1/PlGF ≥ 38	sFlt-1/PlGF < 38	*p-value*
N	60	110	
Maternal age (years) ± (SD)	31.63 ± (6.32)	30.94 ± (6.49)	0.5271*
Skin color			
White	39 (65.00 %)	46 (41.81 %)	**0.0039**
Non-white	21 (35.00 %)	64 (58.19 %)	
Singleton pregnancy	55 (91.67 %)	105 (95.45 %)	0.3260**
Parity			
Nulliparous	21 (35.00 %)	20 (18.18 %)	**0.0143**
Multiparous	39 (65.00 %)	90 (81.82 %)	
Chronic hypertension	29 (48.33 %)	57 (51.82 %)	0.6641
Gestational hypertension	14 (23.33 %)	46 (41.82 %)	**0.0159**
Diabetes	28 (46.67 %)	52 (47.27 %)	0.9397
Obesity (BMI > 30)	41 (68.33 %)	75 (68.18 %)	0.9838
Confirmed COVID-19 during pregnancy	10 (16.67 %)	21 (19.09 %)	0.6957
Preeclampsia (PE)	43 (71.67 %)	57 (51.82 %)	**0.0120**
	n = 43	n = 57	
Interval between the time of blood collection and diagnosis of preeclampsia (days) (95 % CI)	3.44 (−2.94 ~ 9.82)	−23.28 (−32.93 ~ -13.63)	**0.0005****
Systolic BP (mmHg) ± (SD) †	156.33 ± (17.96)	150.59 ± (14.13)	**0.0354***
Diastolic BP (mmHg) ± (SD) †	96.13 ± (11.76)	93.29 ± (9.01)	0.2038*
Oxygen Saturation (%) ± (SD) †	95.42 ± (10.36)	96.25 ± (3.11)	0.1852*
	n = 60	n = 110	
Eclampsia	1 (01.67 %)	0	0.3529**
HELLP syndrome	4 (6.67 %)	3 (2.73 %)	0.1353**
Preterm Birth (< 37 weeks)	33 (55.00 %)	40 (36.36 %)	**0.0190**
	n = 33	n = 40	
Iatrogenic	29 (87.87 %)	34 (85.00 %)	1.0000**
Spontaneous	4 (12.13 %)	6 (15.00 %)	
	n = 60	n = 110	
Delivery Route			
C-section	50 (83.33 %)	87 (79.09 %)	0.5039
Vaginal	10 (16.67 %)	23 (20.91 %)	
5th minute APGAR score < 7	1 (1.67 %)	3 (2.73 %)	1.0000**
Neonatal ICU admission	37 (61.66 %)	31 (28.18 %)	**<0.0001**
SGA	28 (46.66 %)	20 (18.18 %)	**0.0001**
IUGR	11 (18.33 %)	5 (4.55 %)	**0.0033**

*Mann-Whitney test; **Fisher Exact; ***Kolmogorov-Smirnov; †At PE diagnosis

value = 0.3214) (Fig. 2 **A**). PlGF correlates within time in both COVID-19 (−) (***r* = -0.5497, *p-value* < 0.0001**) and COVID-19 (+) cases (***r* = -0.7081, *p-value* < 0.0001**), and the temporal dynamics of both correlations are the same (slopes *p-value* = 0.8882, elevations *p-value* = 0.5310) (Fig. 2 **B**). And sFlt-1/PlGF ratio performs appropriately in COVID-19 (−) (***r* = 0.5493, *p-value* < 0.0001**) and COVID-19 (+) (***r* = 0.6063, *p-value* = 0.0010)**, and repeating the temporal dynamics behavior previously described for the biomarkers alone comparing both groups (slopes *p-value* = 0.6686, elevations *p-value* = 0.7081) (Fig. 2 **C**).

Considering serum samples PE biomarkers levels in COVID-19 (+) confirmed during pregnancy and PE clinical diagnosis (n cases = 16; n samples = 20), the linear correlation model with 3 variables (sFlt-1/PlGF ratio as dependent variable, and Δ Preeclampsia and Δ COVID-19 as independent) exhibit the increasing temporal influence of PE clinical diagnosis onset on sFlt-1/PlGF ratio and no influence of SARS-CoV-2 infection onset overtime (Fig. 3) (Supplemental Data 1). sFlt-1/PlGF ratio 2D linear correlations regarding Δ Preeclampsia (***r* = 0.564, *p-value* = 0.0095**) (Fig. 3 **A**) and Δ COVID-19 (*r = -0.3672, p-value = 0.1112*) (Fig. 3 **B**) were plotted in 2D reassure the finding of the influence of PE in the sFlt-1/PlGF ratio levels, and null correlation of COVID-19 onset. The linear correlation model was plotted as a surface in a 3D scatter plot (Fig. 3 **C**) exhibiting a high fitness model (Model fitness ***p-value* = 0.02483**).

4. Discussion

This study presented the sFlt-1/PlGF ratio evaluated in a SARS-CoV-2 vaccinated cohort of pregnant women with hypertensive disorders. SARS-CoV-2 infection during pregnancy did not impact the biomarkers' temporal dispersion in a high-risk hypertensive disorder population. Considering the sFlt-1/PlGF ratio cutoff of 38, the findings support that this value in association with clinical findings, can still be used to identify cases of PE regardless of COVID-19 status during pregnancy. Similar maternal and perinatal outcomes suggest that SARS-CoV-2 vaccination serves as a protective factor against severe COVID-19 in pregnant women and limits the association with a PE-like syndrome observed in severe COVID-19 cases among SARS-CoV-2 unvaccinated pregnant women.

An overall increased morbidity in the cohort was noted, with increased C-section rates and preterm births. Despite this, adverse perinatal outcomes were rare, most likely due to timely clinical management. No maternal deaths were reported. This underscores the importance of timely and appropriate medical interventions in managing high-risk pregnancies complicated by hypertensive disorders [25,39].

The dynamics and modeling of the sFlt-1 and PlGF biomarkers demonstrated their continued utility in diagnosing PE. The sFlt-1/PlGF ratio effectively distinguished between cases with and without PE (***p-value* = 0.0120**), even in the presence of COVID-19. This reinforces the importance of these biomarkers in clinical practice, particularly for differential diagnosis and management of PE in high-risk pregnancies [40,41].

Altered biomarker levels without a PE diagnosis were observed in some cases, most with underlying risk factors for PE, primarily in chronic hypertension cases, in which the differential diagnosis with superimposed PE is a significant challenge [42,43]. Most likely these cases were delivered prior to the clinical diagnosis of PE (gestational age at birth was around 37 weeks in such cases).

While there has been a recent decline in the overall incidence of severe COVID-19 cases, the prevalence of infection among pregnant women remains substantial, raising ongoing concerns regarding its impact on the rates of hypertensive disorders and PE. The timing of COVID-19 diagnosis and subsequent monitoring pose additional complexities. Prior research has indicated the importance of evaluating the risk of placental insufficiency and the necessity for fetal surveillance in pregnant individuals who contract COVID-19 during the initial trimesters [25,39]. Thus, knowing the COVID-19 exposure during pregnancy remains important for antenatal counseling and ensuring appropriate follow-up procedures to monitor and address potential complications effectively.

Identifying asymptomatic and mild SARS-CoV-2 infections could be a limitation, especially considering vaccination as a protective factor against the morbidity of the disease. However, due to the high-risk

Table 3
Detailed description of sFlt-1/PlGF ≥ 38 (increased ratio) with no clinical diagnosis of preeclampsia.

Case	Maternal age	Parity	Type of Pregnancy	Previous comorbidities	SARS-CoV-2 infection	GA of SARS-CoV-2 infection (weeks)	Fetal Growth Restriction	GA at Childbirth	Adverse pregnancy outcome	Neonatal weight at birth (g)	5 Minutes Apgar	Neonatal Adverse Outcome	Route of Delivery	C-section indication	Higher sFlt-1/PlGF ratio	Prot/Crea
0B.1	29	Multiparous	Singleton	**CH**	No	–	No	38	No	3305	9	No	Vaginal	–	38.18	–
0B.2	27	Multiparous	Singleton	**CH**, Obesity, GDM, Previous Deep Vein Thrombosis	No	–	No	37	No	2770	10	No	C-Section	Bad Obstetric Past	40.50	0.11
0B.3	24	Multiparous	Singleton	**CH**, Obesity, GDM	Yes	16	No	37	Uterine Hypotonia	3150	9	No	C-Section	Bad Obstetric Past	44.99	0.13
0B.4	32	Nulliparous	Singleton	Obesity, GDM, Hypothyroidism, History of Hodking Linfoma	Yes	36	No	38	No	3164	9	No	C-Section	Maternal Pathology	43.78	0.24
0B.5	37	Multiparous	Singleton	**CH**, Obesity, GDM	No	–	No	34	No	2510	7	No	C-Section	–	44.10	–
0B.6	38	Multiparous	Singleton	**CH**, Obesity, GDM, Hypothyroidism	No	–	No	38	No	2560	8	No	C-Section	–	47.85	–
0B.7	33	Multiparous	Singleton	Obesity, GDM	No	–	No	38	No	3280	9	No	Vaginal	–	48.86	0.19
0B.8	34	Multiparous	Singleton	**CH**, SLE, Hypothyrodism, Herpes Infection (3rd Trimester)	No	–	No	37	No	3636	10	No	C-Section	Maternal Pathology	49.04	0.16
0B.9	34	Multiparous	Singleton	**CH**, Obesity, GDM, Asma	No	–	No	37	No	3175	10	No	Vaginal	–	49.62	0.16
0B.10	40	Multiparous	Singleton	**CH**, Obesity, GDM	No	–	No	37	No	2840	9	No	C-Section	Maternal Request	57.17	0.15
0B.11	25	Nulliparous	Singleton	**CH**, GDM	Yes	35	No	39	No	3348	10	No	C-Section	Maternal Request	58.22	–
0B.12	29	Multiparous	Twin	Obesity	No	–	Yes (A); No (B)	37	No	2304 (A); 2370 (B)	10 (A); 09 (B)	No	C-Section	Maternal Pathology	70.00	0.20
0B.13	32	Multiparous	Singleton	**CH**, Obesity, GDM, Hypothyroidism	No	–	No	38	Uterine Hypotonia	3068	9	No	C-Section	Cephalopelvic Disproportion	72.42	0.27
0B.14	40	Multiparous	Singleton	**CH**, Obesity, DM, Herpes Infection	No	–	No	36	No	5155	8	Neonatal Intensive Care Admission, Respiratory Distress	C-Section	Maternal Pathology	75.31	0.23
0B.15	44	Multiparous	Singleton	**CH**, Obesity, GDM	No	–	No	39	No	3020	9	No	C-Section	–	76.73	–
0B.16	30	Nulliparous	Singleton	**CH**, Obesity, GDM, Previous Ischemic Stroke	Yes	37	No	38	No	3085	10	No	Vaginal	–	121.90	0.20
0B.17	37	Nulliparous	Singleton	**CH**, Obesity, DM	No	–	No	39	Uterine Hypotonia	3050	10	No	C-Section	Acute Fetal Distress	199.57	0.26

GDM: gestational diabetes melittus; CH: chronic hypertension; GA: gestational age; PE: preeclampsia; Prot/Crea: Protein/Creatinine ratio.

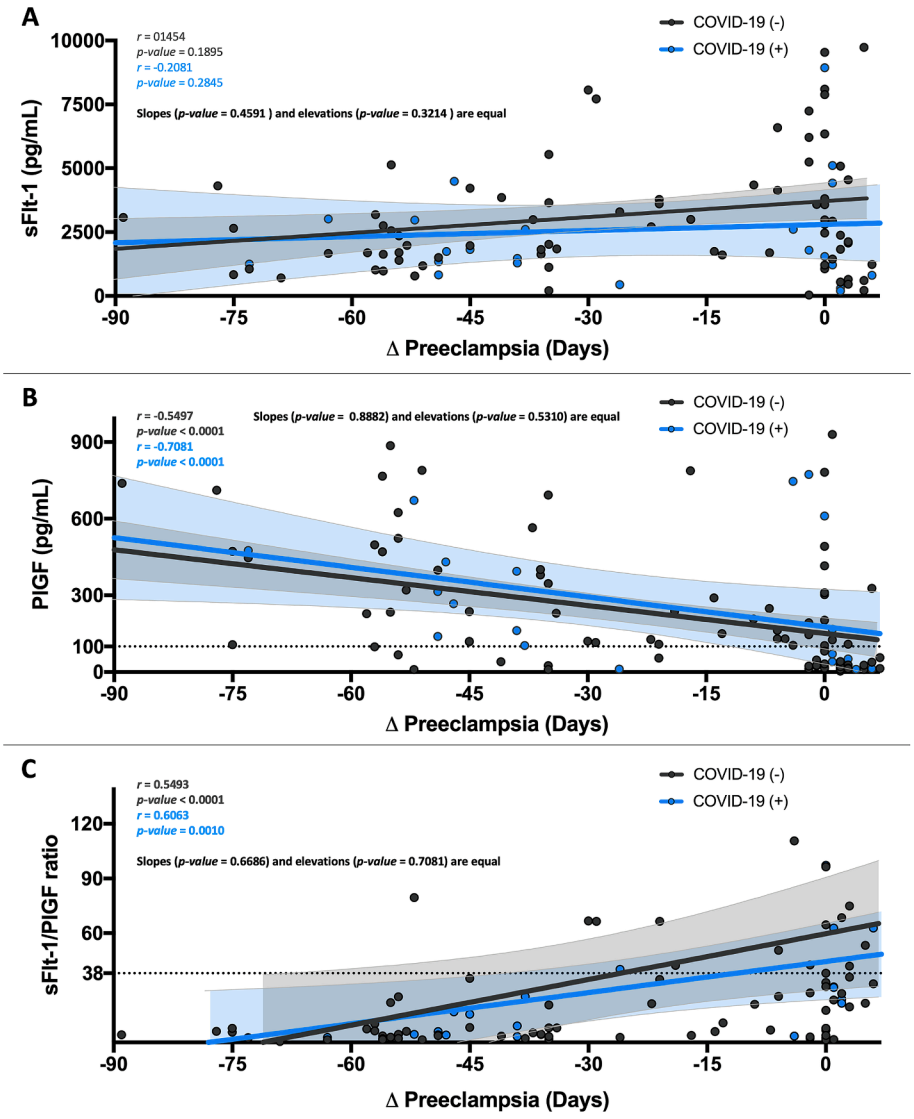

Fig. 2. sFlt-1 (**A**) PlGF (**B**) and sFlt-1/PlGF ratio (**C**) temporal dynamics regarding the difference between serum sample collection date and clinical diagnosis of preeclampsia date in days (Δ Preeclampsia) in COVID-19 (+) (**blue**, n cases = 21, n samples = 30) and COVID-19 (−) (**deep gray**, n cases = 79, n samples = 112) cases during pregnancy. Lines represent linear correlations; area represent error bars 95 % CI; and the dots represent data points of biomarkers sample values. *p-value* ≤ 0.05 considered significant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

nature and close follow-up of the study population, it is expected that symptomatic infections would be more thoroughly screened, thereby minimizing the impact on the analysis. The high-risk profile of the population also may limit the generalizability of the findings; however, it provides valuable insight into COVID-19 and PE interactions in high-risk pregnancies. As a secondary analysis, this study did not include a specific sample size calculation as it relied on the REBRACO cohort, originally powered for broader maternal and perinatal outcomes. Another possible limitation is the timing of sample collection, planned to address COVID-19 exposure. Although a variety of serum sample collection times were included, and some cases had samples collected at a distant point from the clinical diagnosis of PE, which could affect the analysis.

The present results provide detailed clinical outcomes in a high-risk, SARS-CoV-2 vaccinated cohort and PE biomarkers evaluations that add relevant evidence during a milder scenario of COVID-19 and PE. This reinforces the sFlt-1/PlGF ratio as a useful tool for PE differential diagnosis, even in the context of COVID-19 during pregnancy. Nonetheless, awareness about the risk of PE following COVID-19 diagnosis needs to be emphasized, particularly in scenarios with low vaccination coverage and during outbreaks of new viral variants [28]. More adequate pregnancy counseling that incorporates increased patient information in a translational approach should be a key part of clinical management involving high-risk pregnancies and emerging infectious diseases. This approach is essential for improving outcomes and ensuring that pregnant women receive the best possible care in a rapidly changing health landscape [44].

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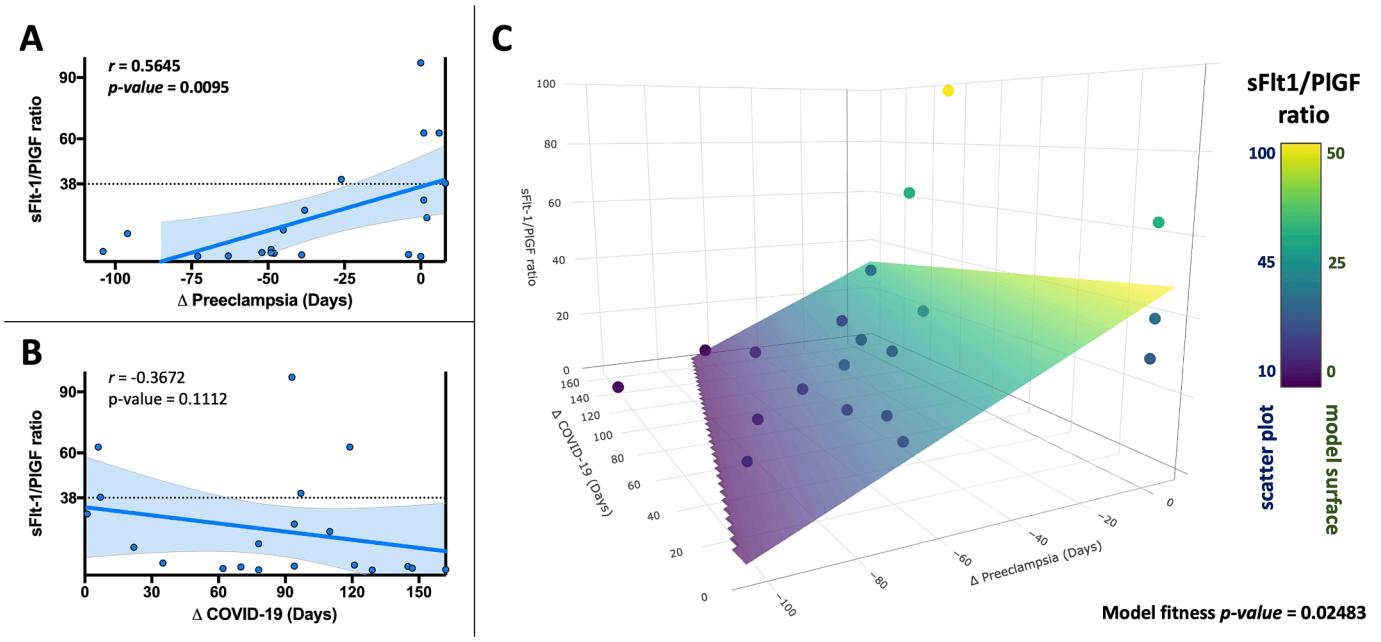

Fig. 3. Linear correlation model with 3 variables: the difference between serum sample collection date and clinical diagnosis of preeclampsia date in days (Δ Preeclampsia); the difference between serum sample collection date and diagnosis of COVID-19 date in days (Δ COVID-19); and sFlt-1/PlGF ratio in serum (n cases = 16; n samples = 20). Δ Preeclampsia (**A**) and Δ COVID-19 (**B**) linear correlations were plotted in 2D, and the linear correlation model was plotted as a surface in a 3D scatter plot (**C**). Lines represent linear correlation (**A, B**); area represent error bars 95 % CI (**A, B**); and the dots represent data points values (**A-C**). *p-value* ≤ 0.05 considered significant.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: IUM serves on the scientific advisory board of Seed Health.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2025.101196.

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