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Preeclampsia among women with COVID-19 during pregnancy and its impact on maternal and perinatal outcomes: Results from a national multicenter study on COVID in Brazil, the REBRACO initiative

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ABSTRACT

Objective: To evaluate the prevalence of preeclampsia among cases of COVID-19 infection during pregnancy and the association between both conditions, in a multicenter cohort of Brazilian women with respiratory symptoms.
Study design: Ancillary analysis of the Brazilian Network of COVID-19 in Obstetrics (REBRACO) study. We performed a nested case-control analysis selecting all women with COVID-19 and compared outcomes between women with and without PE.
Main outcomes: Maternal, gestational, and clinical characteristics and perinatal outcomes.
Measures: Prevalence ratio (PR) and its 95%CI for each of the predictors and outcomes.
Results: A total of 203 women were included: 21 (10.3%) in PE group and 182 (89.7%) in non-PE group. Preeclampsia was not different among women with and without COVID-19 (10.3% vs 13.1%, p-value = 0.41), neither complication such as eclampsia and HELLP syndrome. Chronic hypertension (33.4%) ($p < 0.01$) and obesity (60.0%) ($p = 0.03$) were the most frequent comorbidities in PE group, and they were significantly more frequent in this group. Women with PE had more cesarean section (RR 5.54 [1.33 – 23.14]) and their neonates

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were more frequently admitted to neonatal intensive care unit (PR 2.46[1.06 – 5.69]), most likely due to preterm-birth-related complications.
Conclusion: The prevalence of PE among women with COVID-19 infection during pregnancy was around 10%; women with COVID-19 and a history of chronic hypertension or obesity are more likely to have preeclampsia. Cesarean section is increased among women with PE and COVID-19, with increased rates of neonatal admission to intensive care units, mostly due to prematurity.

1. Introduction

The pandemic of Coronavirus Disease 2019 (COVID-19) was recognized by the World Health Organization (WHO) since early 2020 [1]. The disease is caused by the infection of SARS-CoV-2 ("Severe Acute Respiratory Syndrome – Coronavirus 2), and the angiotensin converting enzyme 2 (ACE2) receptor, expressed in various cellular types, is essential for viral invasion and replication [2].

Renin-angiotensin system plays a fundamental role on blood pressure homeostasis, and angiotensin converting enzyme (ACE) and ACE2 are important components of this pathway. Renin converts angiotensinogen into angiotensin I (Ang-1), which is then converted due to ACE into angiotensin II (Ang-2), an active peptide with significant role in vasoconstriction, fibrosis, proliferation, inflammation, and oxidative stress. Nevertheless, ACE2 converts Ang-2 into Angiotensin-(1–7) (Ang-1–7), another active peptide that plays opposite biological functions (vasodilation, vascular protection, anti-fibrosis, anti-proliferation, and anti-inflammation effects). The balance between ACE and ACE2 guarantees adequate blood pressure homeostasis [3].

ACE2 is highly expressed during pregnancy, remarkably during the third trimester [4]. COVID-19 reduces ACE2 availability, and lower levels of Ang-1–7 are associated to preeclampsia (PE) [5]. Based on this physiological substrate, experimental studies in vitro [6] and few observational studies suggested an association between PE and COVID-19 [7,8].

PE is one of the main determinants of maternal morbidity and death in Brazil [9]. Currently defined as a multi-systemic disease caused by a misbalance between angiogenic factors such as placental growth factor (PlGF) and anti-angiogenic factors, such as soluble factor like tyrokinase 1 (SFLT-1), due to placental chronic hypoxemia secondary to poor placentation during the first half of pregnancy. Clinical manifestation of the disease (hypertension and multi-organic lesions) occur during the second half of pregnancy (from 20 weeks of gestation), as a consequence of endothelial compromise [10].

In Brazil, COVID-19 had a dramatic impact on maternal mortality, with a death rate among women with severe respiratory disease up to 10% in a populational-based registry evaluation during 2020 [11]. We aimed to evaluate the occurence of PE among cases of COVID-19 infection during pregnancy and its association with some maternal, pregnancy, and clinical characteristic besides their maternal and perinatal outcomes, in a national cohort of women with respiratory symptoms.

2. Methods

This study was an ancillary nested case-control analysis of the Brazilian Network of COVID-19 in Obstetrics study (in Portuguese acronymous, REBRACO – Rede Brasileira de COVID-19 em Obstetrícia). REBRACO was a multicenter study that aimed to understand the impact of COVID-19 during pregnancy in a Brazilian obstetric population sample, including 15 maternity hospitals from 4 Brazilian regions. Data collection occurred during 2020 February 1st until 2021 February 28th. The following settings took part of the study: Women's Hospital of the University of Campinas, Sao Paulo (SP); Hospital of Jundiai School of Medicine (SP); Clinics Hospital of Porto Alegre, Rio Grande do Sul (RS); UNIMED Maternity of Belo Horizonte, Minas Gerais (MG); Maternity Hospital of Federal University of Ceara (CE); Hospital of Federal University of Sao Paulo (SP); Moinhos de Vento Hospital of Porto Alegre (RS); Jorge Rossmann Regional Hospital of Itanhaem (SP); Hospital of Federal University of Sao Carlos (SP); Sumare State Hospital (SP); Hospital of Federal University of Minas Gerais (MG); Fernandes Figueira Institute, Rio de Janeiro (RJ); Hospital of the Sao Paulo State University in Botucatu (SP); Hospital of Federal University of Pernambuco (PE); and Santa Casa de Misericordia of Para (PA).

Briefly, REBRACO had five main axes. The first was a cross-sectional study that routinely tested all women for SARS-CoV-2 infection when admitted for childbirth in selected settings, to understand the prevalence of the disease. The second axis was an observational prospective cohort that aimed to evaluate maternal and perinatal outcomes associated with COVID-19 infection during pregnancy. The third axis collected different biological samples of women included in the two previous axes, to constitute a biorepository with linked relevant clinical data on women infected with SARS-CoV-2. The fourth axis established a crisis preparedness and response committee in COVID-19 context, providing data on barriers and facilitators, as well as identifying emerging needs on the pandemic situation. The fifth axis was an ecological study to evaluate overall response to pandemic in different centers included in the REBRACO [12].

For the cohort, all pregnant or postpartum women with flu-like symptoms identified in any of the participating centers were included, and further followed until childbirth and postpartum period. All included women signed an informed consent form before data collection. The research protocol was approved by the Brazilian National Ethics Committee (Letters of Approval numbers 4.047.168, 4.179.679 and 4.083.988) and the protocol was also approved by each local IRBs.

As REBRACO was implemented early in the pandemic, when accurate data on prevalence and severity on pregnancy was not reliable, we did not estimate a sample size, using a convenience sample including all women with symptoms during the study period (February 2020 until February 2021). We also did not include data regarding vaccination because it started in Brazil after data collection period (February 2021 for general population and June 2021 for pregnant women).

Flu-like symptoms considered were fever, cough, shortness of breath, sputum production, nasal or conjunctival congestion, difficulty swallowing, sore throat, runny nose, and clinical signs of respiratory distress or effort, as O_2 saturation $<95\%$, signs of cyanosis, flapping of the nose, intercostal retraction, dyspnea, diarrhea, anosmia and dysgeusia.

Diagnostic testing depended upon local protocols, mostly RT-PCR for SARS-CoV-2; and radiological findings in computerized tomography of COVID-19 in clinical context, was also considered for diagnosis of SARS-CoV-2, according to individual case-analysis and local protocols for each institution.

Clinical, laboratorial, and demographical characteristics, plus maternal and perinatal outcomes were retrieved during follow-up. Those data were obtained by medical charts review performed by trained research assistants in each center. Data were stored in an online web-server (RedCap®), password-protected with different levels of hierarchy.

For this ancillary analysis, we selected all women with COVID-19 confirmed infection (molecular confirmation and/or radiological findings). We excluded women with ongoing pregnancy at the time of this analysis, those with pregnancy loss before 20 weeks gestation, and those with the onset of symptoms after childbirth. Then, we split women into two groups, with PE and without PE, in a nested case-control study

approach. Diagnosis of PE was considered when a woman presented with hypertension (blood pressure higher or equal to 140x90mmHg in two or more measures) after 20 weeks of gestational age, with proteinuria or other laboratorial or clinical signs of endothelial dysfunction had PE.

We also obtained frequency of PE and its complications (eclampsia, Hellp syndrome and imminent eclampsia) among COVID-19 negative women, to estimate the association of the infection with the occurrence of the disease severity, comparing to those with confirmed COVID-19.

We evaluated, among cases of confirmed COVID-19, the occurrence of PE and its complications and further compared cases with and without PE, considering sociodemographic and gestational characteristics, symptoms and clinical presentation at admission, laboratorial findings, risk of severe disease, maternal and perinatal outcomes. We adjusted prevalence of PE and its complication for obesity and chronic hypertension, as those are also risk factors for COVID-19. As the aim of this analysis was to estimate the impact of PE among COVID-19 cases, and the database did not allow for exact identification of timing of onset or diagnosis of PE, we proposed this analysis as nested case-control and all statistical analysis was performed accordingly.

To compare both groups, we applied the Chi-Square test when appropriate for categorical variables (and Fisher's Exact test otherwise). For both tests, we considered a significance of p-value < 0.05. We also obtained prevalence ratio (PR) and risk ratio (RR) and 95% confidence interval for each association. For prevalence of preeclampsia, eclampsia, imminent eclampsia and HELLP syndrome, we presented both unadjusted and adjusted p-value and prevalence ratio. Chronic hypertension and obesity were the variables considered for adjustment. SPSS 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) was the statistical package used for statistical analysis.

3. Results

From the initial 729 symptomatic women included in the database of the study, this analysis considered all confirmed positive cases with data on pregnancy outcomes, including a total of 203 cases, with 21 (10.3%) women with PE and 182 (89.7%) women without PE. Fig. 1 shows the flowchart of included cases, with details on exclusion criteria.

Our first question was if PE is more prevalent among COVID-19 cases during pregnancy and maybe associated to increased severity of PE. Therefore, Table 1 shows the occurrence of PE and its complications among women with and without confirmed COVID-19. PE affected 44 (11.6%) of all symptomatic and tested women, however occurrence was not significant different among those with and without confirmed COVID-19 (10.3% vs 13.1%, p-value = 0.41). Imminent eclampsia was the most frequent complication, while eclampsia and HELLP syndrome were rare events, however similar in both groups. Even after adjustment for chronic hypertension and obesity, prevalence of analyzed conditions was similar among both groups.

Looking into the sociodemographic, previous clinical and obstetric conditions, chronic hypertension and obesity were significantly more frequent in the PE group, as shown in Table 2. Chronic hypertension affected 7 (33.4%) women in the PE group, while the same occurred in 10 (5.5%) women in the non-PE group (RR = 6.07 [2.58 – 14.25]). Obesity was also higher among women with PE, 9 (60.0%) presented the condition, while 42 (32.8%) in the non-PE group (RR = 1.83 [1.13–2.97]). Marital status, source of funding of antenatal care, skin color, trimester of diagnosis of COVID-19, primiparity, and maternal age were similar among groups.

The majority of women in both groups were evaluated in the hospital, due to COVID-19 symptoms, reporting <7 days of such symptoms, as shown in Table 3. It also shows that clinical manifestation of COVID-19-related symptoms were similar in women with and without PE, however tachypnea and desaturation were almost doubled in the PE group (42.1% vs 25.9% and 10.5% vs 5.9%, respectively), although they did not differ significantly. Laboratorial findings of severity were also similar in both groups. Admission to intensive care unit occurred in 6 (30.0%) women in PE group, while 29 (16.2%) women in non-PE group were admitted to the ICU (p-value = 0.12 and RR = 2.01 [0.83 – 4.86]).

Overall pregnancy outcomes were worst among women with PE, as shown in Table 4. Admission to neonatal intensive care unit was higher in this group (47.4%) compared to non-PE group (24.4%) (RR = 2.46 [1.06 – 5.69]). Occurrence of preterm birth had a higher frequency among women with PE (47.6% vs 28.2%), and the same occurred to neonatal respiratory distress, neonatal morbidity and neonatal death, although those differences were not significant, possibly due to the low numbers.

Considering maternal outcomes, Table 4 shows that women with PE had a greater occurrence of cesarean section (RR 5.54 [1.33–23.14]). They also received more magnesium sulphate (47.4% vs 2.5%, RR 11.28 [5.59–22.75]), as this intervention is standardized for severe preeclampsia. Occurrence of maternal haemorrhage and severe maternal outcomes were also higher among women with PE, although again not

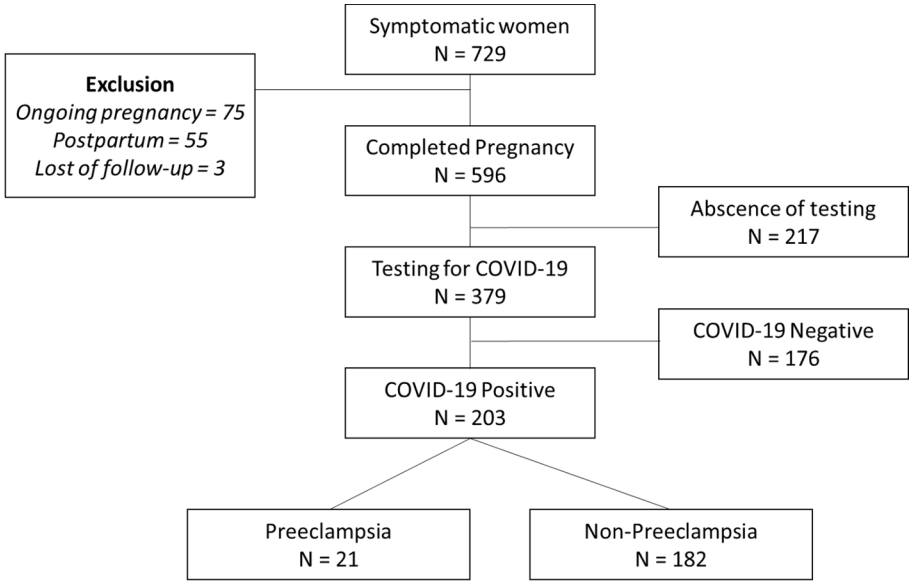

Fig. 1. Flowchart of inclusion of women in this study.

Table 1
Prevalence of Preeclampsia and its severe forms, comparing symptomatic pregnant women that tested positive (COVID-19 Positive) versus those that tested negative for COVID-19 (COVID-19 Negative).

Hypertensive Disorder	COVID-19 Positive	COVID-19 Negative	P-Value	Prevalence Ratio [95%CI]	Adjusted p-value	Adjusted Prevalence Ratio [95% CI]
Preeclampsia	21 (10.3)	23 (13.1)	0.409	0.88 [0.63 – 1.21]	0.281	0.81 [0.57 – 1.16]
Eclampsia	1 (0.5)	0 (0)	0.350	**1.87 [1.71 – 2.06]**	0.982	**1.96 [1.74 – 2.21]**
HELLP*	2 (1.0)	4 (2.3)	0.320	0.62 [0.20 – 1.93]	0.339	0.54 [0.17 – 1.68]
Imminent Eclampsia**	5 (2.5)	6 (3.4)	0.584	0.84 [0.44 – 1.62]	0.826	0.85 [0.44 – 1.64]

HELLP: occurrence of elevated liver enzymes and hemolysis and low platelets count; Imminent eclampsia: women presenting headache or visual symptoms or upper-abdominal pain. P-value and Prevalence Ratio were adjusted for the following variables: chronic hypertension and obesity.

Table 2
Sociodemographic, previous clinical and obstetric conditions characteristics of symptomatic women with confirmed COVID-19, according to the occurrence of preeclampsia.

Variable	Preeclampsia +	Preeclampsia -	P-Value	Risk Ratio (IC)
N	21	182		
Maternal age			0.30	1.44 [0.75 – 2.80]
≤35 years	14 (66.7)	140 (76.9)		
> 35 years	7 (33.3)	42 (23.1)		
Trimester of Diagnosis of COVID-19			0.59	
First	1 (4.8)	22 (12.1)		
Second	5 (23.8)	44 (24.2)		
Third	15 (71.4)	116 (63.7)		
Skin Color			0.76	0.94 [0.61 – 1.44]
White	11 (52.4)	100 (55.9)		
Non-White	10 (47.6)	79 (44.1)		
Marital Status			1.00	1.00 [0.53 – 1.88]
Single	7 (35.0)	63 (35.0)		
Married	13 (65.0)	117 (65.0)		
Antenatal Care			0.58	1.08 [0.85 – 1.36]
Public	16 (80.0)	127 (74.3)		
Private	4 (20.0)	44 (25.7)		
Primigravida	9 (42.9)	57 (31.5)	0.29	1.36 [0.79 – 2.33]
Chronic Hypertension	7 (33.4)	10 (5.5)	**<0.01**	**6.07 [2.58 – 14.25]**
Obesity	9 (60.0)	41 (32.8)	**0.03**	**1.83 [1.13 – 2.97]**

Table 3
Clinical and laboratorial manifestations at inclusion of symptomatic women with confirmed COVID-19, according to the occurrence of preeclampsia.

Variable	Preeclampsia +	Preeclampsia -	P-Value	Risk Ratio [IC]
N	21	182		
Time from onset of symptoms (days)			0.72	
<7	15 (75.0)	121 (71.2)		Ref
≥7	5 (25.0)	49 (28.8)		1.05 [0.80 – 1.31]
Tachypnea	8 (42.1)	42 (25.9)	0.13	1.62 [0.90 – 2.92]
Desaturation	2 (10.5)	10 (5.9)	0.42	1.78 [0.42 – 7.52]
SGOP ≥ 70 (Admission)	1 (6.2)	4 (5.4)	0.89	1.15 [0.14 – 9.67]
Any SGOP ≥ 70	4 (28.6)	10 (15.1)	0.23	1.88 [0.69 – 5.16]
SGTP ≥ 70 (Admission)	1 (6.7)	4 (5.7)	0.89	1.17 [0.14 – 9.71]
Any SGTP ≥ 70	2 (15.4)	6 (9.5)	0.62	1.61 [0.37 – 7.13]
Platelets count < 100,000	3 (25.0)	13 (14.4)	0.39	1.73 [0.57 – 5.20]
Creatinine > 1.2 mg/dL	1 (6.7)	4 (4.9)	0.78	1.35 [0.16 – 11.26]
Admission to ICU	6 (30.0)	29 (16.2)	0.12	2.01 [0.83 – 4.86]

SGOP: glutamic oxaloacetic transaminase; SGTP: glutamic piruvic transaminase; ICU: intensive care unit.

significant.

4. Discussion

We aimed to understand the impact of PE in women with COVID-19, evaluating results from a Brazilian national study. Our results showed that the prevalence of PE was high, however did not differ among women with and without confirmed COVID-19 (around 10%). We also presented that COVID-19 positive pregnant women with chronic hypertension and obese had a higher prevalence of PE, and clinical and laboratorial manifestations at the onset of symptoms were not accurate to predict the occurrence of PE. Our results also support the hypothesis that women with COVID-19 and PE have increased adverse maternal and perinatal outcomes when comparing to those with only COVID-19.

Some studies have previously estimated the prevalence of PE in Brazil, however there is not a reliable national database. Prevalence is around 7.5%, as estimated by a national cohort of only primigravida women without underlying severe risk factors [13]. In our study, overall frequency of PE among women with COVID-19 was 10.3%. One study performed in United States of America [14] showed a similar prevalence of PE (10.4%), however they included all Sars-COV-2 positive women, regardless of symptoms. Another study, conducted in the United Kingdom [15], obtained a prevalence of 10.5% of PE, however they included only 23 women.

A study performed in Mexico [16] demonstrated that COVID-19 positive women had a higher prevalence of PE (18% vs 9%, OR 2.2 (1.00 – 5.2)). This study included 240 pregnant women with flu-like symptoms and compared women with a positive test of COVID-19 (70) versus 170 women with negative test of COVID-19, and pre-eclampsia was the only condition associated with COVID-19 infection. Another robust international multicenter study, with 706 positive women and 1424 negative women [17] obtained a prevalence of 8.4% of PE among positive women, while the prevalence of PE among negative women was 4.4% (OR 1.76 (1.27 – 2.43)). Our results did not show a significant association between COVID-19 infection and PE. Nevertheless, we should point out that in our population, the negative cases were symptomatic women that further tested negative for COVID-19 and we do not have a sample of asymptomatic negative cases, which could be considered for a more consistent baseline prevalence of PE. In that regard, we may add that some symptoms of PE are overall greatly ignored and much associated to worse outcomes, such as shortness of breath and desaturation, which are also symptoms for suspected COVID-19. This might explain why among symptomatic cases that tested negative, there was a 13% prevalence of PE.

Our results supported the association between chronic hypertension and obesity with PE, among women with COVID-19. Obesity and chronic hypertension are already recognized chronic comorbidities associated to the occurrence and severity of COVID-19 [18,19]. Our findings supported that concurrent conditions may impact on the severity of both diseases. Unfortunately, we did not collect data on the

Table 4
Pregnancy outcomes of symptomatic women with confirmed COVID-19, according to the occurrence of preeclampsia.

Variable	Preeclampsia +	Preeclampsia -	P-Value	Risk Ratio (IC)
N	21	182		
Severe Maternal Outcome*	6 (28.6)	29 (15.9)	0.147	1.92 [0.80 – 4.60]
Fetal Death	0 (0)	7 (96.0)	0.448	–
Maternal Death	2 (9.5)	9 (4.9)	0.318	1.84 [0.49 – 6.91]
Use of Magnesium Sulphate	9 (47.4)	4 (2.5)	**<0.01**	**11.28 [5.59 – 22.75]**
Maternal Haemorrhage	4 (19.0)	13 (7.1)	0.08	2.57 [0.98 – 6.79]
Preterm Birth	10 (47.6)	50 (28.2)	0.07	2.09 [0.94 – 4.66]
Provider-initiated preterm birth	8 (80.0)	32 (64.0)	0.47	2.00 [0.47 – 8.56]
Mode of Delivery			**<0.01**	
Cesarean Section	19 (90.5)	106 (59.9)		**5.54 [1.33 – 23.14]**
Vaginal Delivery	2 (9.52)	71 (40.1)		
Low Birthweight	4 (19.0)	38 (23.3)	0.79	0.79 [0.28 – 2.23]
Apgar 5° <7	1 (4.8)	7 (4.2)	0.624	1.02 [0.78 – 1.32]
Neonatal Respiratory Distress	7 (38.9)	34 (21.2)	0.092	2.13 [0.88 – 5.13]
Admission to Neonatal ICU	9 (47.4)	40 (24.4)	**0.032**	**2.46 [1.06 – 5.69]**
Neonatal Morbidity	2 (9.5)	7 (3.8)	0.230	2.27 [0.62 – 8.28]
Neonatal Death	2 (10.5)	5 (3.1)	0.159	2.92 [0.83 – 10.26]

history of prophylaxis for PE, however, it is important to highlight that aspirin and calcium should be implemented early in antenatal care, in women with such conditions. There are currently no recommendations against these medications during COVID-19 infection [20].

All these data lead us to the following discussion: does COVID-19 induce a PE-like syndrome [21]? Or do COVID-19 and PE have the same risk factors for severity? Previous evidence support that SARS-CoV-2 directly impact kidneys, increasing serum creatinine and urea levels as well as increasing the occurrence of proteinuria and hematuria [22]. Soluble factor like tyrokinase-1 (sFLT-1) is increased in cases of pneumonia due to COVID-19, but placental growth factor (PlGF) levels are stable; however, the sFLT-1/PlGF ratio can increase [23]. Unbalance between those two angiogenic factors plays an important role on PE. We believe that this unbalance may be harmful to women who are already at high risk to develop PE, and COVID-19 may increase their already high-risk, triggering the occurrence of PE.

Women with PE presented overall worse maternal and perinatal outcomes when compared with those without PE. We believe that, adding sample size and maybe in future combined analysis, some variables would meet statistical significance, especially maternal admission to intensive care unit, preterm birth, neonatal respiratory distress, neonatal morbidity, and neonatal death. Data collection for this study included COVID-19 cases in Brazil, up to the beginning of 2021, but ended before the worse period in number and severity of cases in the country, as well as the introduction of new SARS-CoV-2 variants.

Preterm birth deeply impacts on other perinatal outcomes, such as neonatal respiratory distress, neonatal morbidity, and neonatal death. Results from the other two similar studies presented diverging results: while Villar [17] showed an increased risk for preterm birth (in a sample of 2,130 women, comparing 706 positive women against 1424 negative women), Cardona-Perez [16] (in a sample of 240 women, comparing 70 positive women against 170 negative women) estimated similar occurrence in both groups. In our results, almost half of women with COVID-19 and PE underwent a preterm medically indicated childbirth, through cesarean section. We must improve the present capacity to diagnose among PE, severe PE and severe COVID-19 with organ dysfunction that could mimic the diagnosis of PE. Gestational age plays a key role in such findings and decision upon possible expectant management. The role of biomarkers in such differential diagnosis might be an interesting approach and should be further studied. Clinical implementation of biomarkers in obstetric care could identify women with PE and COVID-19 and those with only COVID-19, helping clinicians to avoid unnecessary preterm births. Anyway, even if not significant, the rate of preterm birth among PE women with Covid19 positive was twice higher than those without PE.

Our study has a few limitations, such as that our database does not allow us to determine if the diagnosis of PE occurred before or after the COVID-19 infection. Another limitation is that some Brazilian regions were not included. In addition, this study had a limited sample size. However, as far as we know, our study is the first to prospectively gather data of COVID-19 and preeclampsia in a sample of obstetric population in Brazil.

5. Conclusions

The prevalence of PE among women with COVID-19 infection during pregnancy was around 10%; women with COVID-19 and a history of chronic hypertension or obesity are more likely to develop preeclampsia. Cesarean section is increased among women with PE and COVID-19, with an increased likelihood of neonatal admission to intensive care units, mostly due to prematurity.

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