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COVID-19 and Its Association with Hypertensive Disorders of Pregnancy and Preterm Birth: A Retrospective Cohort Study

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Abstract

Background: COVID-19 during pregnancy has been associated with various obstetric complications; however, epidemiological evidence regarding its relationship with hypertensive disorders of pregnancy (HDP) and preterm birth remains inconclusive. Therefore, we aimed to evaluate the association between COVID-19 during pregnancy and the risk of HDP and preterm birth among Mexican pregnant women. **Methods:** We conducted a retrospective cohort study based on a review of 3710 medical records of women treated at a tertiary hospital between 2020 and 2023. COVID-19 was diagnosed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay. We estimated adjusted risk ratios (aRRs) using robust Poisson regression models, controlling for potential confounders. **Results:** The COVID-19 rate was 2.5%. We observed that women with COVID-19 had a higher risk of HDP (aRR = 1.59; 95% CI = 1.07–2.36). When HDP subgroups were analyzed separately, COVID-19 was associated with an increased risk of preeclampsia (aRR = 2.04; 95% CI = 1.34–4.20) and preterm birth (aRR = 1.50; 95% CI = 1.02–2.19). The association with gestational hypertension lost statistical significance after adjustment. **Conclusions:** Our findings suggest that COVID-19 during pregnancy may be associated with hypertensive disorders of pregnancy and preterm birth. However, the observed association with preeclampsia should be interpreted cautiously because diagnostic overlap between severe COVID-19 and preeclampsia cannot be excluded.

Keywords: COVID-19; hypertensive disorders of pregnancy; premature birth; pregnancy



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1. Introduction

Hypertensive disorders of pregnancy (HDP) are among the most significant groups of obstetric complications worldwide. These disorders, which include gestational hypertension, preeclampsia, and eclampsia, affect approximately 5% to 10% of pregnancies and are a leading cause of maternal and perinatal morbidity and mortality [1]. HDP has been associated with multiple serious complications, including multi-organ damage, renal failure, fetal growth restriction, preterm birth, and maternal death. Furthermore, women with a

history of HDP have an increased risk of developing cardiovascular disease in the long term [2,3].

On the other hand, preterm birth, defined as birth before 37 completed weeks of gestation, remains a leading cause of neonatal mortality globally [4]. It is estimated that approximately 1 in 10 births occurs preterm [5], and this outcome has been linked to major neonatal complications, including respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and long-term neurodevelopmental disorders [6].

HDP and preterm birth share several pathophysiological mechanisms, including systemic inflammation, endothelial dysfunction, and impaired placental perfusion [2,3,7].

COVID-19 has also been associated with systemic inflammation, endothelial dysfunction, and thrombotic alterations [8,9]. Furthermore, the virus enters host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in placental tissue and plays an important role in vascular homeostasis during pregnancy [10]. Disruption of these pathways has been proposed as a potential mechanism linking COVID-19 with adverse obstetric outcomes, including HDP and preterm birth [11,12].

However, epidemiological evidence regarding the association between COVID-19 and HDP remains inconsistent. Some studies have reported that women with this infection have an increased risk of developing preeclampsia and other hypertensive disorders of pregnancy [13–15]. In contrast, other research has found no statistically significant associations between COVID-19 and these hypertensive disorders [15–21]. Moreover, some findings suggest that the magnitude and consistency of these associations may vary depending on the specific type of hypertensive disorder being assessed, particularly between gestational hypertension and preeclampsia.

Similarly, the evidence regarding the relationship between COVID-19 and preterm birth remains heterogeneous. Several studies have reported an increased risk of preterm birth among women infected with SARS-CoV-2 during pregnancy [22–25]. Conversely, other research has documented associations in the opposite direction, although these did not reach statistical significance [26–29].

In addition, preterm birth among women with COVID-19 may be either spontaneous or medically indicated (iatrogenic). In some cases, preterm delivery may result from maternal clinical deterioration or pregnancy complications such as hypertensive disorders of pregnancy, which require early delivery to reduce maternal and fetal risks. Such a distinction may partly contribute to the heterogeneity of findings reported across studies [12].

These discrepancies could be explained by differences in the timing of infection during pregnancy, the clinical severity of COVID-19, the diagnostic strategies used, and the degree of adjustment for potential confounding factors. Furthermore, most existing studies were conducted during the early waves of the pandemic, before widespread vaccination and significant changes in the clinical management of the disease. In exploratory analyses stratified by pandemic period, we observed some variation in the magnitude of the associations across different phases of the pandemic, particularly for hypertensive disorders of pregnancy. However, these findings should be interpreted cautiously because of the limited number of women with COVID-19 within each stratum and the exploratory nature of these analyses.

Despite the growing body of international evidence, data from Latin American populations remain relatively limited [12]. This is particularly relevant because the burden of maternal comorbidities, access to healthcare services, and the organization of obstetric care may differ from those reported in high-income countries, potentially influencing both the occurrence and management of COVID-19-related obstetric complications. Therefore, additional evidence from regional settings is needed to better understand the potential impact of COVID-19 on maternal and perinatal health outcomes.

Although COVID-19 was no longer considered a global public health emergency in 2023, SARS-CoV-2 continues to circulate globally and poses a clinical challenge in vulnera-

ble populations, including pregnant women. In this context, understanding its potential impact on obstetric outcomes remains relevant for identifying higher-risk maternal groups, strengthening prenatal surveillance, and generating useful evidence for future infectious emergencies with similar inflammatory and vascular mechanisms. Hence, we evaluated the association between COVID-19 during pregnancy and the risk of HDP and preterm birth among Mexican women receiving obstetric care at a tertiary care hospital between 2020 and 2023.

2. Materials and Methods

2.1. Design and Study Population

We conducted a retrospective cohort study based on a review of the medical records of women who underwent pregnancy termination at a tertiary care hospital in Mexico City between April 2020 and December 2023. This hospital serves as a referral center for obstetric and medical patients with complex needs.

The study population consisted of pregnant women treated at the institution during the study period. Women aged 18 years or older with singleton pregnancies and medical records containing information on COVID-19 status during pregnancy, gestational age at birth, and relevant clinical and sociodemographic variables were included in the analysis. Multiple pregnancies, women under 18 years of age, records without confirmatory SARS-CoV-2 testing, and records with incomplete information needed to define exposure, primary outcomes, or essential covariates were excluded.

2.2. Study Variables and Collection

The independent variable was the presence of COVID-19 during pregnancy, defined as a documented SARS-CoV-2-positive quantitative reverse transcription polymerase chain reaction (qRT-PCR) test recorded in the medical record. The primary outcomes were HDP and preterm birth. Hypertensive disorders of pregnancy (HDP), including gestational hypertension, preeclampsia, and eclampsia, were identified directly from diagnoses recorded in medical records as part of routine care. However, due to the very low frequency of eclampsia cases in the cohort ($n = 6$) and the fact that none of these cases occurred among women with COVID-19, the analyses focused solely on gestational hypertension and preeclampsia. Diagnoses were made by obstetricians and gynecologists according to the American College of Obstetricians and Gynecologists (ACOG) criteria in effect during the study period, which include hypertension accompanied by proteinuria and/or signs of maternal end-organ dysfunction. To identify hypertensive disorders occurring during pregnancy, women with a history of chronic or pre-existing hypertension were excluded from these analyses. Preterm delivery was defined as birth before 37 completed weeks of gestation.

Covariates included maternal sociodemographic and clinical characteristics potentially associated with COVID-19 or adverse obstetric outcomes, such as maternal age, educational level, monthly income, parity, pre-pregnancy body mass index, smoking during pregnancy, and medical history documented in the medical record. The gestational trimester at COVID-19 diagnosis was also identified from the medical records and classified as first, second, or third trimester according to the gestational age recorded at the time of the positive qRT-PCR test.

Following approval from the ethics and research committees, we collected data retrospectively from physical medical records, as the hospital where the study was conducted does not have an electronic health record system. Records that met the requirements were reviewed manually, and the information obtained was subsequently digitized in a database specifically designed for this study.

To ensure data quality and inter-rater reliability during data extraction, a pilot validation exercise was conducted before the final construction of the database. Two researchers

independently reviewed a random sample corresponding to 10% of the total study population, and agreement on the main study variables was assessed using Cohen's kappa coefficient. Adequate agreement was observed between the evaluators ($\kappa = 0.71$).

2.3. Statistical Analysis

The characteristics of the study population and the events of interest were summarized using absolute frequencies and percentages for categorical variables. In contrast, quantitative variables were described using medians and interquartile ranges because they did not follow a normal distribution, as indicated by the Kolmogorov–Smirnov test. To estimate the cumulative frequency of each event of interest, the number of women who experienced the event was divided by the total number of women included in the corresponding analysis. We also compared the frequency of interest between women with and without COVID-19. Additionally, among women with COVID-19, an exploratory analysis was performed comparing the frequency of adverse obstetric outcomes according to intensive care unit admission status as a proxy for disease severity. Pearson's chi-squared test was used for these comparisons.

To examine the association of interest, independent Poisson regression models with robust variance were constructed for each event of interest (HDP and preterm birth), from which relative risks (RR) with their respective 95% confidence intervals were estimated. This approach was preferred to logistic regression because odds ratios can overestimate the magnitude of the association when outcomes are frequent, particularly when their frequency exceeds 5–10%. For analyses involving HDP, women with pre-existing chronic hypertension were excluded to evaluate hypertensive disorders occurring during pregnancy.

As a sensitivity analysis, we evaluated whether the association between COVID-19 and the study outcomes varied by pandemic period (2020–2021 and 2022–2023). For this purpose, an interaction term between COVID-19 and study period was included in the Poisson regression models to assess effect modification on the multiplicative scale.

All models were adjusted for potential confounding factors selected using directed acyclic graphs (DAGs). Therefore, we constructed an independent DAG for each outcome of interest, including HDP and preterm birth. For HDP, the minimal sufficient adjustment set included age, monthly family income, parity, smoking, education level, pre-existing diabetes, pre-pregnancy body mass index, and year of care (Figure S1). Meanwhile, for preterm birth, the corresponding adjustment set included age, monthly family income, parity, smoking, education level, and pre-existing hypertension (Figure S2). To explore the potential influence of unmeasured confounders on the observed associations, E values were calculated for the associations between COVID-19 during pregnancy and the outcomes of interest. The E value represents the minimum magnitude of association that a potential unmeasured confounder could have with both the exposure and the outcome, independent of covariates already included in the models, that would be required to fully explain the observed associations.

Statistical significance was defined as $p < 0.05$. All analyses were conducted using STATA version 19.5 (StataCorp, College Station, TX, USA).

3. Results

During the study period, 4391 deliveries were recorded, of which 616 were to mothers under 18 years of age, and 65 were multiple pregnancies. Therefore, this analysis was based on a review of 3710 delivery records.

The general characteristics of the study population are summarized in Table 1. The median age of the women was 25 years, and the highest level of education was lower secondary education. In total, 10.3% reported tobacco use and 5.5% reported alcohol consumption.

Less than 2% had pre-existing hypertension or diabetes. As for obstetric history, 40% were primiparous. Accordingly, 5.2% (among multiparous women) and 2.0% reported a history of gestational hypertension and preterm delivery, respectively. During the study period, 2.5% of the women tested positive for COVID-19.

Table 1. General characteristics and COVID-19 cases of the study population.

Characteristics	Total (n = 3710)
Age (in years)	
Median (IQR)	25 (9)
Marital status, n (%)	
No partner	102 (2.8)
With partner	3608 (97.2)
Family monthly income (USD)	
Median (IQR)	491 (71)
Education level, n (%)	
Primary education	365 (9.8)
Lower secondary education	1909 (51.5)
Upper secondary education	786 (21.2)
Tertiary secondary education	650 (17.5)
Alcohol consumption, n (%)	
No	3505 (94.5)
Yes	204 (5.5)
Cigarette smoking, n (%)	
No	3328 (89.7)
Yes	382 (10.3)
Pre-pregnancy BMI, n (%)	
Underweight	79 (2.1)
Normal weight	1563 (42.1)
Overweight	1372 (37.0)
Obesity class I	641 (17.3)
Obesity class II	55 (1.5)
Parity f (%)	
Nulliparous	1446 (39.0)
1–2	1844 (49.7)
≥3	420 (11.3)
Pre-existing chronic hypertension, n (%)	
No	3668 (98.9)
Yes	42 (1.13)
Pre-existing diabetes, n (%)	
No	3647 (98.3)
Yes	63 (1.7)
History of gestational hypertension, n (%) ^a	
No	2144 (94.7)
Yes	120 (5.3)
History of preterm birth, n (%)	
No	3636 (98.0)
Yes	74 (2.0)
Year of care, n (%)	
2020	150 (4.0)
2021	661 (17.8)
2022	1290 (34.8)
2023	1609 (43.4)
COVID-19 during pregnancy, n (%)	
No	3617 (97.5)
Yes	93 (2.5)

Table 1. *Cont.*

Characteristics	Total (n = 3710)
COVID-19 vaccination (≥ 1 dose), n (%)	
No	174 (4.7)
Yes	3536 (95.3)
ICU admission, n (%)	
No	3584 (96.6)
Yes	126 (3.4)

Abbreviations: ICU, intensive care unit. ^a Available only for women with previous pregnancies.

Most COVID-19 cases occurred during the first two years of the pandemic (2020–2021), accounting for 73.1% of all infections. Likewise, ICU admissions among women with COVID-19 were concentrated mainly during this period, while COVID-19 vaccination coverage increased substantially from 2021 onwards. Among women diagnosed with COVID-19 during pregnancy, 5.4% of infections occurred in the first trimester, 9.7% in the second, and 85.0% in the third.

In the study population, the frequency of HDP was 10.2%. When the different subtypes were analyzed, gestational hypertension was present in 6.3% of cases, while preeclampsia was observed in 3.7% of the women included in the study. Although six cases of eclampsia were identified in the overall cohort, none occurred among women with COVID-19.

Women with COVID-19 had a higher frequency of hypertensive disorders of pregnancy, including both gestational hypertension and preeclampsia (Table 2).

Table 2. Hypertensive disorders of pregnancy according to COVID-19 status.

Outcome	COVID-19			<i>p</i> -Value ^a
	Total (n = 3710)	No	Yes	
Hypertensive disorders of pregnancy, n (%)				
No	3331 (89.8)	3266 (90.3)	65 (69.9)	<0.001
Yes	379 (10.2)	351 (9.7)	28 (30.1)	
Type of hypertensive disorder				
Gestational hypertension, n (%)				
No	3475 (93.7)	3396 (93.9)	79 (85.0)	<0.001
Yes	235 (6.3)	221 (6.1)	14 (15.0)	
Preeclampsia, n (%)				
No	3572 (96.3)	3492 (96.6)	80 (86.1)	<0.001
Yes	138 (3.7)	125 (3.4)	13 (13.9)	

^a *p*-values were obtained using Pearson's chi-squared test.

When comparing the history of COVID-19 during pregnancy, we observed that women with COVID-19 had a higher rate of preterm birth than those without a history of this infection (Table 3).

Table 3. Preterm birth according to COVID-19 status.

Outcome	COVID-19			<i>p</i> -Value ^a
	Total (n = 3710)	No	Yes	
Preterm birth, n (%)				
No	3421 (92.2)	3351 (92.6)	65 (75.3)	<0.001
Yes	289 (7.8)	266 (7.4)	23 (24.7)	

^a *p*-value was obtained using Pearson's chi-squared test.

When the association between COVID-19 and the presence of HDP was assessed, women with COVID-19 had an approximately threefold increased risk of developing

these disorders compared with those without COVID-19 (RR = 3.02; 95% CI = 2.12, 4.28; $p < 0.001$). After adjusting for potential confounders, the association remained statistically significant, although the effect size was attenuated (RR = 1.59; 95% CI = 1.07, 2.36; $p = 0.021$). When the analysis was repeated for each type of hypertensive disorder, a similar pattern was observed. However, the association between COVID-19 and gestational hypertension lost statistical significance after adjustment for covariates (RR = 1.37; 95% CI = 0.77, 2.54; $p = 0.288$) (Table 4). The E-values for the associations between COVID-19 and HDP and preeclampsia were 2.56 and 3.850, respectively, indicating that an unmeasured confounder would need to be associated with both COVID-19 and these outcomes, with risk ratios of at least these magnitudes, independent of the measured covariates, to fully explain the observed associations.

Table 4. Crude and adjusted risk ratios of the association between COVID-19 and hypertensive disorders in pregnancy.

Outcomes	RR (95% CI)	<i>p</i> -Value	RR (95% CI) ^a	<i>p</i> -Value
Hypertensive disorders of pregnancy				
No	Ref.	-	Ref.	-
Yes	3.02 (2.12–4.28)	<0.001	1.59 (1.07–2.36)	0.021
Gestational hypertension				
No	Ref.	-	Ref.	-
Yes	2.57 (1.54–4.30)	<0.001	1.37 (0.77–2.54)	0.288
Preeclampsia				
No	Ref.	-	Ref.	-
Yes	3.58 (1.95–6.57)	0.022	2.04 (1.34–4.20)	0.037

Abbreviations: Ref., reference; RR, risk ratio; CI, confidence interval. ^a Adjusted for age, monthly family income, parity, smoking, education level, pre-existing diabetes, pre-pregnancy body mass index, and year of care.

On the other hand, it was observed that women with COVID-19 had an approximately 3.5 times greater risk of preterm delivery compared to those without such infection (RR = 3.52; 95% CI = 2.45, 5.07; $p < 0.001$). After adjustment for potential confounding factors, the association remained statistically significant, although with a smaller effect size (RR = 1.50; 95% CI = 1.02, 2.19; $p = 0.037$) (Table 5). The E-value for this association was 2.37, suggesting that an unmeasured confounder would need to be associated with both COVID-19 and preterm birth by a risk ratio of at least 2.37 each, independently of the measured covariates, to explain the observed association fully.

Table 5. Crude and adjusted risk ratios of the association between COVID-19 and Preterm birth.

Outcomes	RR (95% CI)	<i>p</i> -Value	RR (95% CI) ^a	<i>p</i> -Value
Preterm birth				
No	Ref.	-	Ref.	-
Yes	3.52 (2.45–5.07)	<0.001	1.50 (1.02–2.19)	0.037

Abbreviations: Ref., reference; RR, risk ratio; CI, confidence interval. ^a Adjusted for age, monthly family income, parity, smoking, education level, and pre-existing hypertension.

In an exploratory analysis restricted to women with COVID-19, those requiring intensive care unit admission had a significantly higher frequency of preterm birth (71.4% vs. 16.5%; $p < 0.001$) and hypertensive disorders of pregnancy (41.4% vs. 17.2%; $p = 0.012$) compared with women who did not require intensive care unit admission (Table S1).

Additional exploratory analyses stratified by pandemic period (2020–2021 vs. 2022–2023) suggested that the association between COVID-19 and hypertensive disorders of pregnancy may have varied across pandemic phases, whereas no clear differences were observed for preterm birth (Tables S2 and S3). Given the limited number of exposed women within some strata, these findings should be interpreted with caution.

4. Discussion

In this retrospective cohort study, COVID-19 infection during pregnancy was associated with an increased risk of hypertensive disorders of pregnancy, preeclampsia, and preterm delivery. These findings add to the growing body of evidence suggesting that viral infections during pregnancy may contribute to the development of maternal and perinatal obstetric complications.

In our study, the proportion of COVID-19 cases from 2020 to 2023 was 2.5%; this figure is comparable to other retrospective studies based on clinical record reviews, which have reported prevalences between 2 and 3% [30]. Nevertheless, our COVID-19 rate is lower than that reported in population studies and meta-analyses, which estimate prevalence between 5% [31] and 9% [32]. Therefore, some asymptomatic infections may not have been identified, which may have contributed to an underestimation of the true prevalence of COVID-19 in our study population.

We also found that the accumulated incidence of HDP was 10.2%, while that of gestational hypertension and preeclampsia was 6.3% and 3.7%, respectively. These data are comparable to those reported in the previous literature, which has documented that hypertensive disorders are one of the main complications in pregnancy, estimated to occur in 5% to 10% of cases [1]. In our study, the incidence is at the upper limit of the range, which may be explained by the characteristics of the population treated at a tertiary care hospital, where more complex clinical cases are more likely to be treated. It is also relevant to mention that the frequency of gestational hypertension was higher than that of preeclampsia, which is consistent with what has been described in the previous literature. This pattern is to be expected, since gestational hypertension represents a more frequent and, in general, less severe form within the group of hypertensive complications that can occur during pregnancy. Conversely, preeclampsia, although more clinically severe, occurs less frequently [3].

On the other hand, in this analysis, we observed that the frequency of hypertensive disorders was higher among women with COVID-19. In the adjusted models, we found a positive and statistically significant association between COVID-19 and hypertensive disorders of pregnancy. When we stratified the associations by type of hypertensive disorder, we observed associations in the same direction; however, only the association with preeclampsia remained statistically significant.

To date, previous studies linking COVID-19 to the development of HDP remain inconclusive. Some studies conducted in 2020 in North American and Chinese women reported inverse associations between COVID-19 and the risk of preeclampsia; however, these associations did not reach statistical significance [16,17]. In contrast, other studies conducted in 2021 in India [13], the United States [14], and England [15] reported that, after adjusting for confounding factors, COVID-19 is associated with a significantly increased risk of preeclampsia. On the other hand, studies conducted during the first waves of the pandemic in Iranian [33], Mexican [34], Chinese [20], and British [21] women did not find statistically significant associations; however, the direction of the observed associations suggested a possible increased risk of preeclampsia among women with COVID-19.

Regarding gestational hypertension, the results of previous studies have also been inconsistent. A study conducted in Portugal reported an inverse, though not statistically significant, association between COVID-19 and gestational hypertension [35]. In contrast, studies conducted in the United States reported positive but not statistically significant associations between these variables [18,19]. In our study, the association remained significant for preeclampsia but not for gestational hypertension after adjustment for confounding factors. This finding suggests that the crude association may have been partially explained by differences in maternal characteristics and baseline risk factors between women with and without COVID-19. It is also possible that gestational hypertension and preeclampsia, although

related conditions, differ in their underlying pathophysiological mechanisms and susceptibility to the inflammatory and endothelial alterations associated with SARS-CoV-2 infection. Furthermore, the relatively small number of women with COVID-19 may have limited the precision of the estimates, reducing the ability to detect more modest associations.

Overall, the available evidence suggests that the association between COVID-19 and gestational hypertension has not been consistently demonstrated.

In this context, our findings are similar to studies reporting a significant association between COVID-19 and preeclampsia, and they also align with evidence indicating inconclusive or non-significant results for gestational hypertension after adjustment for confounding factors. Moreover, previous meta-analyses and multicenter studies have reported conflicting findings regarding the association between COVID-19 and preeclampsia, with some reporting an increased risk and others finding no statistically significant association [12,36]. Several methodological and clinical factors, including differences in study design, timing and severity of infection, diagnostic criteria, and adjustment for confounding variables, may explain the discrepancies between our results and those reported in the literature. In addition, severe COVID-19 may present with clinical and laboratory manifestations that overlap with the diagnostic criteria used for preeclampsia, including endothelial dysfunction, proteinuria, thrombocytopenia, and hepatic or renal injury. Hence, some women with COVID-19 may have fulfilled clinical criteria for preeclampsia despite presenting a preeclampsia-like syndrome associated with SARS-CoV-2 infection rather than classical placental disease. This possibility may have been particularly relevant during the early stages of the pandemic, when most infections in our cohort occurred and when clinical knowledge and diagnostic approaches were still evolving. Therefore, these findings suggest that the relationship between COVID-19 and hypertensive disorders of pregnancy is complex and likely depends on the specific disorder being evaluated, the characteristics of the study population, and the clinical context in which diagnoses are established.

Despite the aforementioned differences, several biological mechanisms have been proposed to explain the relationship between COVID-19 and hypertensive disorders of pregnancy. It has been suggested that this virus induces a pro-inflammatory, hypercoagulable state, accompanied by endothelial dysfunction, which can impair adequate placental perfusion [15,37,38]. These changes are particularly relevant, as disorders such as preeclampsia share similar pathophysiological mechanisms, including endothelial damage, systemic inflammation, and alterations in angiogenesis [39]. Furthermore, the virus's interaction with the renin-angiotensin system, through its binding to the ACE2 receptor, could contribute to an imbalance in blood pressure regulation, creating an environment conducive to the development of hypertension during pregnancy [40].

In our study, the association remained significant for preeclampsia but not for gestational hypertension after adjustment for confounding factors. This finding may reflect differences in the underlying pathophysiology of these conditions. Although both belong to the spectrum of hypertensive disorders of pregnancy, preeclampsia is characterized by more pronounced placental and vascular dysfunction. Therefore, COVID-19 may have a greater impact on pathways involved in the development of preeclampsia than on those associated with gestational hypertension [15]. These differences may also help explain the positive association observed between COVID-19 and HDP as a whole.

On the other hand, the preterm birth rate observed in our study was 7.7%, which is consistent with the range previously reported in the international literature [5]. We also observed that women with COVID-19 had a higher probability of experiencing preterm birth, and this association was statistically significant in both the crude and adjusted models for confounding factors.

These findings are similar to those reported in a study of German women, which found that the preterm birth rate was significantly higher during the first two years of the COVID-19 pandemic (2020–2021) than in the pre-pandemic period (2017–2019) [41]. Similarly, other studies conducted in the United States [24,25], England [23], and Hong Kong [22] have shown that COVID-19 infection significantly increases the risk of preterm birth. Consistent with these findings, a systematic review and meta-analysis reported that women with COVID-19 had 48% higher odds of preterm birth than non-infected women [42].

Nonetheless, some studies have reported inverse associations. For example, studies conducted in Brazil [26], Italy [27], India [28], and the United States [29] reported that women with COVID-19 had a lower risk of preterm birth; however, these associations did not reach statistical significance. Taken together, the available evidence suggests that the association between COVID-19 and preterm birth remains heterogeneous across studies, although several investigations have reported an increased risk among infected women.

One possible explanation for the association between COVID-19 and preterm birth is the systemic inflammatory response triggered by the infection. During pregnancy, increased inflammatory mediators can activate pathways associated with the onset of labor, promoting uterine contractions, cervical changes, and premature rupture of membranes. In addition, the infection can affect placental function through alterations in perfusion and thrombotic events, compromising adequate maternal-fetal exchange [43,44].

Moreover, in our exploratory analysis limited to women with COVID-19, those who required ICU admission had a higher frequency of HDP and preterm births compared to women who did not require intensive care. These findings are consistent with previous studies suggesting that more severe forms of COVID-19 during pregnancy may be associated with a higher incidence of adverse obstetric outcomes [24,45]. A possible explanation for these findings is that more severe forms of COVID-19 may be associated with a higher frequency of systemic complications, which could increase the risk of adverse obstetric outcomes [15,45].

From a public health perspective, our findings may be particularly relevant for Mexico and other Latin American countries, where healthcare systems faced substantial challenges during the COVID-19 pandemic and maternal morbidity remains a significant concern. Although the magnitude of the observed associations should be interpreted cautiously, our results support the importance of maintaining close obstetric surveillance among pregnant women with COVID-19, especially those presenting severe disease or additional risk factors for adverse pregnancy outcomes.

Limitations and Strengths

Our study has limitations that must be considered when interpreting our results. First, because of its retrospective design based on medical records, there is a risk of misclassification of both exposures and outcomes. However, because the diagnosis of COVID-19 was based on documented RT-PCR-confirmed cases recorded in medical records, asymptomatic infections that were not tested or documented may have gone undetected, potentially leading to an underestimation of the true prevalence of infection in the study population. Furthermore, given the observational and retrospective nature of the study, the estimated associations should not be interpreted as causal and must be interpreted with caution.

Another important limitation is the lack of homogeneous, detailed information on the clinical severity of COVID-19 infection across all patients, particularly during the first waves of the pandemic, when diagnostic and hospitalization criteria were still evolving. In addition, some manifestations of severe COVID-19, including endothelial dysfunction, proteinuria, thrombocytopenia, and hepatic or renal injury, may overlap with clinical and laboratory features used in the diagnosis of preeclampsia. Consequently, some women may have

presented a preeclampsia-like syndrome associated with SARS-CoV-2 infection, potentially leading to outcome misclassification. This possibility may be particularly relevant during the early stages of the pandemic, when most COVID-19 cases in our cohort occurred. In this context, laboratory markers associated with COVID-19 severity, such as the neutrophil-to-lymphocyte ratio, were not consistently available in the medical records and therefore could not be evaluated. As a result, admission to the obstetric intensive care unit was used as an indirect indicator of greater clinical severity. However, admissions to the intensive care unit among patients with COVID-19 were concentrated mainly in 2020 and 2021; hence, exploratory analyses of severity should be interpreted with caution.

Additionally, although the overall sample size was large, the number of women with COVID-19 was relatively small. Therefore, estimates involving infected women, particularly those related to hypertensive disorders of pregnancy and preeclampsia, should be interpreted with caution because of the limited number of exposed participants. Consequently, some estimates were accompanied by relatively wide confidence intervals, reflecting statistical imprecision.

Furthermore, while information on the year of care and COVID-19 vaccination was available, these variables were primarily considered as adjustment covariates. Hence, this study was not designed to specifically assess the independent effect of vaccination or different stages of the pandemic on the obstetric outcomes analyzed. Additionally, information on the specific SARS-CoV-2 variant responsible for each infection was not available. This limitation is relevant because different viral variants circulating during the study period may have differed in their clinical severity and potential impact on obstetric outcomes. Likewise, information on other viral infections during pregnancy was not systematically available in the medical records and therefore could not be evaluated. Moreover, given the observational nature of the study, residual confounding from unmeasured or incompletely recorded variables cannot be completely ruled out. However, models were adjusted for multiple clinically relevant confounders, and E-values were also estimated to assess the potential influence of unmeasured confounders.

Finally, we conducted this study at a single tertiary hospital, which may limit the generalizability of our findings to other populations or care settings. However, there is no clear biological basis to suggest that the inflammatory and endothelial mechanisms potentially involved in the association among COVID-19, HDP, and preterm birth differ substantially across populations.

Despite the limitations, our study also has strengths. First, we included a large sample of women treated at a tertiary hospital, allowing us to simultaneously assess various relevant obstetric outcomes, including hypertensive disorders of pregnancy and preterm birth. Moreover, the study period spanned virtually the entire duration of the COVID-19 health emergency, including phases before and after the widespread implementation of vaccination, providing a broader view of the association between COVID-19 and obstetric complications across the pandemic.

5. Conclusions

Our findings suggest that COVID-19 during pregnancy may be associated with an increased frequency of hypertensive disorders of pregnancy and preterm birth. However, the observed association with preeclampsia should be interpreted with caution because some manifestations of severe COVID-19 may mimic preeclampsia, potentially contributing to diagnostic overlap. Further studies with detailed clinical and laboratory characterization are needed to clarify whether this association reflects a true increase in preeclampsia risk or, in part, a preeclampsia-like syndrome related to SARS-CoV-2 infection.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/covid6070110/s1>, Figure S1: DAG for the association between COVID-19 and hypertensive disorders in pregnancy; Figure S2: DAG for the association between COVID-19 and preterm birth; Table S1: Frequency of adverse obstetric outcomes according to intensive care unit admission among women with COVID-19 during pregnancy; Table S2: Association between COVID-19 during pregnancy and hypertensive disorders of pregnancy according to pandemic period (2020–2021 vs. 2022–2023); Table S3. Exploratory analysis of the association between COVID-19 during pregnancy and preterm birth according to the pandemic period.

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Data Availability Statement: The data that support the findings of this study are openly available in Mendeley Data (doi: 10.17632/dp7rddbvn3.1; <https://data.mendeley.com/datasets/dp7rddbvn3/1>, accessed on 12 May 2026).

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Abbreviations

The following abbreviations are used in this manuscript:

ACOG	American College of Obstetricians and Gynecologists
ACE2	Angiotensin-Converting Enzyme 2
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DAG	Directed Acyclic Graphs
HDP	Hypertensive Disorders of Pregnancy
ICU	Intensive Care Unit
IQR	Interquartile Range
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RR	Risk Ratios
aRR	Adjusted Risk Ratio
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

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