Original Article

# Risk of preeclampsia in patients with symptomatic COVID-19 infection

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A B S T R A C T

*Objectives:* Recent studies suggest an association between COVID-19 infection during pregnancy and preeclampsia. Nonetheless, these studies are subject to numerous biases. We compared the onset of preeclampsia in a group with symptomatic COVID-19 during pregnancy to that in a group whose non-exposure to the virus was certain, in a center where pregnancy management was identical in both groups.
*Study Design:* This was a single-center study comparing exposed and unexposed patients. The exposed group included pregnant women with symptomatic COVID-19 infection (diagnosed by RT-PCR or CT scan), who gave birth between March and December, 2020. The unexposed group included pregnant women who gave birth between March and December, 2019. Only cases of preeclampsia that occurred after COVID-19 infection were considered. A multivariate analysis was performed to study the existence of an association between COVID-19 and preeclampsia. A sensitivity analysis was performed among nulliparous patients.
*Results:* The frequency of preeclampsia was 3.2% (3/93) in the exposed group, versus 2.2% (4/186) in the unexposed group ($P = 0.58$). Among the nulliparous patients, the frequency of preeclampsia was 4.9% (2/41) in the exposed group versus 0.9% (1/106) in the unexposed group ($P = 0.13$). The association between COVID-19 and preeclampsia was not significant after multivariate analysis (OR 3.12, 95% CI 0.39-24.6).
*Conclusion:* Symptomatic COVID-19 infection during pregnancy does not appear to increase the risk of preeclampsia strongly, although the size of our sample prevents us from reaching a conclusion about a low or moderate risk. It therefore does not appear necessary to reinforce preeclampsia screening in patients with symptomatic COVID-19 infection during pregnancy.

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## Introduction

SARS-CoV-2 infection has been associated with unexpected issues, beyond respiratory complications and increased mortality in pregnant women (1–4). Recent studies have mentioned an association between preeclampsia and COVID-19, with preeclampsia reported among 4.8% to 10% of women infected during pregnancy (3–11). An interaction between SARS-CoV-2 and the renin-angiotensin-aldosterone system (RAAS) during the host infection has been suggested to explain this association. Indeed, the binding of SARS-CoV-2 to the ACE2 receptors may diminish the levels of angiotensin 1-7 and produce a vasoconstrictive, proinflammatory, and procoagulant effect, leading to placental vascular lesions and the onset of preeclampsia (12–15).

Although numerous studies have been published on this topic, several biases affect their interpretation (16). The most important concerns the classification bias presented by asymptomatic COVID-positive pregnant women included in the control groups; asymptomatic cases account for 47% to 60% of all COVID-19 infections, depending on the study (17,18). On the other hand, depending on whether COVID-19 screening is routine or targeted only at symptomatic women, the probability of being positive in these different studies can vary substantially, especially among women with preeclampsia. Finally, these studies usually do not consider either the risk factors for preeclampsia between the COVID-positive and -negative groups, or the chronology of the onset of preeclampsia compared with that of COVID-19 infection.

The objective of our study was to look for the existence of an association between a symptomatic COVID-19 infection during pregnancy and the onset of preeclampsia, using a control group in which the absence of COVID-19 infection was certain.

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## Material and methods

This retrospective exposed/unexposed cohort study took place at the Port Royal Maternity Hospital, a level-3 university hospital in Paris, France, where 5500 deliveries occur annually.

### Study population

All the patients included received prenatal care at the maternity ward from the beginning of their pregnancy. The exposed group included symptomatic pregnant women who tested positive for COVID-19 with prenatal care and delivery between March 1, 2020, and December 31, 2020, at the Port Royal Maternity Hospital. We then compared each woman in the exposed group to two unexposed women with the same pregnancy start date, but a year earlier, to ensure that this group would not include any women with an asymptomatic COVID-19 infection. The unexposed group thus included women whose prenatal care and delivery took place at Port Royal before the pandemic, i.e., between March 1 and December 31, 2019. The inclusion criteria were identical in the exposed and unexposed groups, with the exception of COVID-19 infection.

Patients were excluded from the study if they were asymptomatic but had tested positive for COVID-19 or had been diagnosed with preeclampsia before their COVID-19 infection; if they had been transferred for care in our hospital before delivery (in utero transfers), to avoid overestimating the frequency of either preeclampsia or COVID-19 infection. Patients were also excluded if they had a multiple pregnancy, as it is associated with a higher risk of preeclampsia, but also because excluding multiple pregnancies allowed us to have a more homogenous study population. Multiple pregnancies have enhanced prenatal care, and their management can be different from that of singleton pregnancies, especially concerning COVID-19 screening. Since we could not take into account these differences, we preferred to exclude multiple pregnancies from our study.

Clinical data were routinely collected in real time in the patients' medical records. Data were then extracted retrospectively for the study and merged into a single, anonymized database.

This study was approved by the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL n° 1755849). Under French regulations, this study is exempt from IRB review because it is an observational study using anonymized data from medical records. Women are informed that their records can be used for the evaluation of medical practices and are provided the option to opt out of these studies.

### Screening practices for COVID-19 and for preeclampsia

The maternity unit used the following screening strategy for COVID-19 during the inclusion period: women with symptoms suggestive of a COVID-19 infection (fever, coughing, rhinorrhea, headaches, anosmia, agueusia) were screened at the hospital or at a local private medical laboratory. Women diagnosed positive for COVID-19 were systematically listed in a file by a department physician assigned to maintain this list. When the test was performed at a private laboratory, the patient was instructed to inform the hospital if the result was positive. In the absence of symptoms, no routine screening tests were performed on admission to the hospital or the delivery room. COVID-19 infection was diagnosed by a reverse transcriptase-polymerase chain reaction (RT-PCR) positive for SARS-CoV-2 from nasopharyngeal swabs (limit of detection was 40 cycles, kits used were from GeneXpert®, Abbott Real-Time SARS-COV-2), or by a chest computed tomography (CT) scan with images strongly suggestive of the SARS-CoV-2 lung disease [19]. Except for the first 14 days of contagiousness, during which staff telephoned the women daily, standard monthly prenatal care continued. COVID-19 infection during pregnancy was not an indication for enhanced prenatal care.

Regular screening for preeclampsia took place during each monthly prenatal consultation, by measuring blood pressure and using a urinary dipstick to test for proteinuria. The methods of screening for and the definition of preeclampsia were identical in 2019 and 2020.

### Principal and secondary assessment criteria

The principal endpoint was the onset of preeclampsia, defined as blood pressure equal to or greater than 140 and/or 90 mmHg, together with proteinuria equal to or greater than 0.3 grams/24 hours after 20 weeks of gestation. Only women with preeclampsia that occurred after their COVID infection were included.

The secondary outcome measures were the onset of vascular fetal growth restriction, defined by an estimated fetal weight below the 10th percentile with abnormal fetal and/or maternal Doppler findings [20,21]. Umbilical artery Doppler velocimetry was considered abnormal when the resistance index exceeded the 97th percentile, while uterine artery Doppler findings were considered abnormal when the resistance index exceeded the 97th percentile or bilateral notches were present [22]. We also studied obstetric and neonatal outcomes: gestational age at birth (in weeks of gestation), mode of delivery, birth weight (in grams), growth restriction (defined by a birth weight below the third percentile of the EPOPé curves [21]), and the umbilical artery pH at birth.

### Factors studied

We assessed the following factors: maternal age, parity, history of chronic hypertension (defined as treated hypertension), preexisting diabetes (type 1 or type 2), chronic respiratory disease (asthma, cystic fibrosis, sleep apnea syndrome, or other obstructive or restrictive pulmonary disease), body mass index (BMI, in kilograms/m$^2$), smoking during pregnancy, geographic origin, socio-occupational category, aspirin treatment during pregnancy, and history of fetal growth restriction or preeclampsia during a previous pregnancy.

The characteristics of COVID-19 infection in the exposed group were described by degree of severity: oxygen therapy, invasive ventilation, ICU admission, or cesarean for COVID-19 infection.

### Statistical analysis

The results for continuous (quantitative) variables were expressed as medians with their interquartile ranges and for categorical (qualitative) variables as numbers and as percentages. The exposed and unexposed groups were compared with the Mann-Whitney test for the quantitative variables and with the Chi-2 test or Fisher's exact test, as appropriate for the qualitative variables. The threshold of significance was set at $P < 0.05$. The statistical analysis used Stata 13.0 software.

We then performed a multivariate logistic regression model, which included factors that may be associated with preeclampsia: age > 35 years, geographic origin, BMI $\geq$ 30 kg/m$^2$, history of preeclampsia, chronic hypertension, diabetes (type 1 or 2). This model enabled us to obtain adjusted ORs (aOR) and their 95% CIs. The statistical analysis also used Stata 13.0 software. Statistical significance was defined as $P < 0.05$.

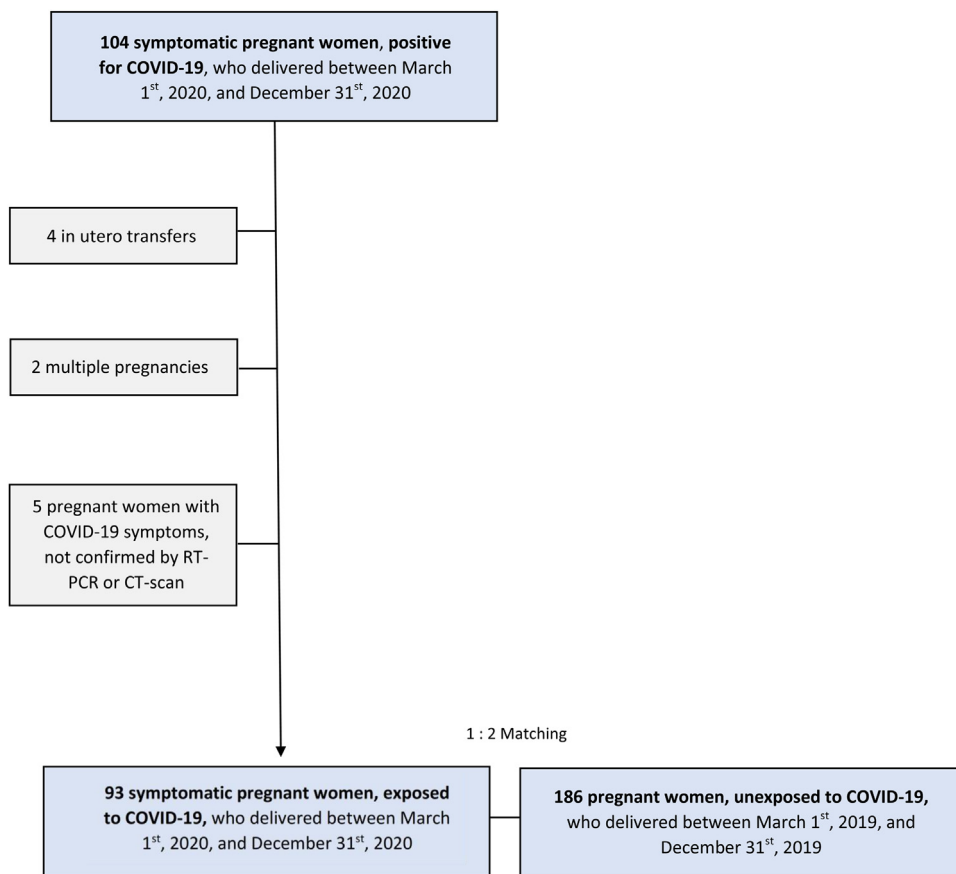A sensitivity analysis was performed among the nulliparous women.

**Fig. 1.** Flow-chart of the exposed and unexposed women (N= 279)

## Results

The exposed group included 93 women with a symptomatic COVID-19 infection during pregnancy, and the unexposed group 186 women selected during their inclusion period (Fig. 1).

The women in the exposed and unexposed groups were comparable, in particular in terms of comorbidities, age, and body mass index (Table 1). On the other hand, there were significantly more nulliparas in the unexposed group (56.9%) than in the exposed group (44.1%) ($P = 0.04$). The positive diagnosis of COVID-19 infection was made by RT-PCR in 99% of cases (92/93), while the CT scan was very suggestive of SARS-CoV-2 lung disease for one woman despite a negative RT-PCR result (Table 2). Median gestational age at diagnosis of COVID-19 infection was 32 weeks of gestation (interquartile range [28-35])

Five women (5.4%) were infected with COVID-19 during the first trimester of pregnancy, and nine (9.7%) before 20 weeks of gestation. Fifteen women (16.1%) with a COVID-19 infection were hospitalized: 11 in standard hospitalization (11.8%), and 4 (4.3%) in the ICU. Five women required oxygen therapy, one was intubated, with ECMO (extracorporeal membrane oxygenation) required after a cesarean delivery. Two women (2.2%) had an emergency cesarean for respiratory deterioration associated with severe COVID-19 infection. No women died.

Preeclampsia was observed in 3.2% of the women (3/93) in the exposed group versus 2.2% (4/186) in the unexposed group ($P = 0.58$). The sensitivity analysis of the nulliparous women showed no significant difference between the groups: 4.9% (2/41) of the nulliparas in the exposed group had preeclampsia versus 0.9% (1/106) in the unexposed group ($P = 0.13$) (Table 3). No woman with severe COVID-19 had preeclampsia.

We did not observe a significant difference in the onset of fetal growth restriction in either the overall study population ($P = 0.52$) or among the nulliparas ($P= 0.53$) (Table 3).

Most women had vaginal deliveries: 83.9% (78/93) in the exposed group and 77.9% (145/186) in the unexposed group ($P = 0.25$). Among the neonatal outcomes, gestational age at birth was similar in the two groups: 39.5 weeks of gestation in the exposed group, and 39.4 weeks in the unexposed group ($P = 0.61$). Birth weight was identical in both groups, with a similar incidence of growth-restriction ($P > 0.99$). There were no in utero fetal deaths (Table 3). The obstetric and neonatal outcomes were also similar among the nulliparous women.

After multivariate analysis, COVID-19 infection was not significantly associated with preeclampsia (aOR 3.12, 95% CI 0.39-24.60) (Table 4).

## Discussion

The incidence of preeclampsia after COVID-19 infection during pregnancy was not significantly higher in our study than among uninfected women

Several studies have reported a significant association between COVID-19 and preeclampsia, but methodological limitations impede the interpretation of their results. An international multicenter study observed nearly twice as many cases of preeclampsia among 725 women exposed to COVID-19 during pregnancy than among 1459 unexposed women (5). More recently, a systematic review and meta-analysis on COVID-19 was published, including 11 studies and 42,754 COVID-19 positive pregnant women. The incidence rate of preeclampsia was 7% among these patients, with a significant increased risk of 1.6 (11) Nonetheless, in these

**Table 1**

Demographic characteristics of women with a COVID-19 infection during pregnancy, compared with uninfected women (N=279)

| Women's characteristics | COVID-19 exposure status | | |
| --- | --- | --- | --- |
| | Exposed (N=93) | Unexposed (N=186) | P |
| **Age (years)** | 33 [30-36] | 32 [30-35] | 0.51 |
| **Nulliparous** | 41 (44.1) | 106 (56.9) | 0.04 |
| **Prepregnancy BMI (kg/m2)** | 22 [20-24] | 22 [20-25] | 0.66 |
| between 25-30 kg/m² | 11 (11.8) | 30 (16.1) | 0.34 |
| > 30 kg/m2 | 12 (12.9) | 18 (9.7) | 0.41 |
| **Active smoking** | 2 (2.2) | 14 (7.5) | 0.07 |
| **History of** | | | |
| Chronic hypertension | 2 (2.2) | 1 (0.5) | 0.22 |
| Diabetes (type 1 or type 2) | 0 | 3 (1.6) | 0.22 |
| Chronic respiratory disease | 1 (1.1) | 9 (4.8) | 0.11 |
| Preeclampsia[1] | 3 (5.8) | 3 (3.8) | 0.38 |
| Fetal growth restriction[1] | 6 (11.6) | 9 (11.3) | 0.57 |
| **Geographic origin** | | | 0.43 |
| White | 64 (68.9) | 124 (66.7) | |
| sub-Saharan Africa | 8 (8.6) | 26 (13.9) | |
| West Indies/Caribbean | 3 (3.2) | 3 (1.6) | |
| North Africa | 15 (16.1) | 23 (12.4) | |
| Asia | 0 | 4 (2.2) | |
| Other | 3 (3.2) | 6 (3.2) | |
| **Socio-occupational category** | | | 0.21 |
| Business owners, executives, managers | 41 (44.1) | 74 (39.8) | |
| Intermediate white-collar occupations, shopkeepers, office, sales, and service workers, tradespeople | 43 (46.2) | 79 (42.5) | |
| Farmers, blue collar workers, the unemployed, students | 9 (9.7) | 33 (17.7) | |
| **Took aspirin during pregnancy[2]** | 4 (4.3) | 8 (4.3) | 1.00 |

BMI: Body mass index.

[1] Percentages among the parous and multiparous patients (N=52 for the exposed group, N=80 for the unexposed group). [2]Aspirin 100 mg/dayThe results for continuous variables were expressed as medians with their interquartile ranges and for categorical variables as numbers and percentages. The interquartile ranges are reported inside square brackets, percentages inside parentheses.

**Table 2**

Characteristics of symptomatic women with positive COVID-19 test results (N=93)

| | Women with symptomatic COVID-19 infection (N=93) |
| --- | --- |
| Gestational age at infection with COVID-19 | 32 [28-35] |
| **Hospitalization:** | 15 (16.1) |
| Standard hospitalization for COVID-19 | 11 (11.8) |
| ICU admission for COVID-19 | 4 (4.3) |
| **Respiratory management:** | |
| Oxygen therapy | 5 (5.4) |
| Intubation | 1 (1.1) |

The results for continuous variables were expressed as medians with their interquartile ranges and for categorical variables as numbers and percentages.

The interquartile ranges are between square brackets, percentages between parentheses.

**Table 3**

Obstetric and neonatal outcomes in the groups exposed and unexposed during pregnancy, in all women (N=279) and in nulliparas (N=147)

| **All women (N=279)** | COVID-19 exposure status | | |
| --- | --- | --- | --- |
| | Exposed (N=93) | Non-exposed (N=186) | P |
| Preeclampsia | 3 (3.2) | 4 (2.2) | 0.58 |
| Fetal growth restriction | 1 (1.1) | 4 (2.2) | 0.52 |
| **Nulliparous women (N=147)** | **Exposed (N=41)** | **Non-exposed (N=106)** | **P** |
| Preeclampsia | 2 (4.9) | 1 (0.9) | 0.13 |
| Fetal growth restriction | 0 | 1 (0.9) | 0.53 |
| **Obstetric outcome (N=279)** | **Exposed (N =93)** | **Non-exposed (N=186)** | **P** |
| Vaginal delivery | 78 (83.9) | 145 (77.9) | 0.25 |
| Cesarean delivery | 15 (16.1) | 41 (22.1) | 0.29 |
| Maternal deaths | 0 | 0 | - |
| **Neonatal outcome (n)** | **Exposed (N =93)** | **Non-exposed (N=186)** | **P** |
| Term at birth (weeks) | 39.5 [38.6-40.5] | 39.4 [38.5-40.5] | 0.61 |
| Birth weight (g) | 3260 [2990-3560] | 3260 [2970-3570] | 0.96 |
| Fetal growth restriction | 3 (3.2) | 6 (3.2) | 1.00 |
| Arterial pH at birth | 7.27 [7.22-7.32] | 7.27 [7.21-7.31] | 0.26 |

weeks: weeks of gestation; g: grams

The results for continuous variables were expressed as medians with their interquartile ranges) and for categorical variables as numbers and percentages.

The interquartile ranges are inside square brackets, percentages inside parentheses.

**Table 4**

Variables associated with the risk of preeclampsia: multivariate analysis including risk factors for preeclampsia and for COVID-19 infection (N = 279).

| Variables | aOR | 95%CI |
|---|---|---|
| **COVID-19 infection** | | |
| No, n=186 | Ref. | |
| Yes, n=93 | 3.12 | [0.39-24.60] |
| **Age > 35 years** | | |
| > 35 years, n=66 | Ref. | |
| ≤ 35 years, n=213 | 5.23 | [0.16-224.17] |
| **Parity** | | |
| Parous, n = 132 | Ref. | |
| Nulliparous n=147 | 2.74 | [0.28-27.28] |
| **Geographic origin** | | |
| Other, n=245 | Ref. | |
| Sub-Saharan Africa, n = 34 | 11.47 | [1.25-105.44] |
| **BMI (kg/m2)** | | |
| <30 (kg/m$^2$), n = 249 | Ref. | |
| ≥30 (kg/m$^2$), n = 30 | 11.61 | [1.67-80.64] |
| **History of preeclampsia** | | |
| No, n=273 | Ref. | |
| Yes, n=6 | 20.61 | [0.64-664.52] |
| **Chronic hypertension** | | |
| No, n=276 | Ref. | |
| Yes, n=3 | 1.07 | [0.01-93.41] |
| **Diabetes (type 1 or type 2)** | | |
| No, n=276 | Ref. | |
| Yes, n=3 | 57.12 | [1.61-2023.92] |

aOR: adjusted odds ratio. Ref : reference.

After multivariate analysis, COVID-19 infection was not significantly associated with preeclampsia (aOR 3.12, 95% CI 0.39-24.60) (Table 4).

studies, the screening strategies were heterogeneous, with some centers requiring routine screening at admission, while others screened only patients with symptoms. It is thus possible that some of the centers participating in these international studies routinely performed COVID-19 screening on all patients admitted for preeclampsia, increasing their probability of positive COVID-19 results compared to women who were not hospitalized, especially during the pandemic period. Moreover, these studies did not specify the chronology of the onset of preeclampsia compared with COVID-19 infection. Finally, the rate of findings positive for COVID-19 was underestimated in the unexposed groups because of the absence of routine screening.

Another meta-analysis of 28 studies also reported a significant association between preeclampsia and COVID-19 infection (9). Nonetheless it used very broad diagnostic criteria for preeclampsia, which it defined by arterial hypertension, either preexisting or appearing after 20 weeks of gestation, associated with a variety of anomalies − either laboratory (hepatic cytolysis, thrombocytopenia, or proteinuria), or clinical (pulmonary edema or neurological complication) after 20 weeks of gestation. Proteinuria was not a mandatory diagnostic criterion for preeclampsia. With the broad American definition for preeclampsia, it can make it difficult to distinguish between COVID-19 infection and the onset of preeclampsia, as these two entities share similarities, especially laboratory anomalies. That is, thrombocytopenia, hepatic cytolysis, and kidney damage are all potential complications of COVID-19 that suggest a "preeclampsia-like syndrome" (23).

Other studies, however, have not shown any association between COVID-19 and preeclampsia. An observational cohort study including more than 250 COVID-positive women observed no association between COVID-19 and preeclampsia, regardless of disease severity (24). In the same way, a national multicenter study on COVID-19 in Brazil, showed that the prevalence of preeclampsia did not differ among women with and without confirmed COVID-19 (around 10%) (25). Our results also point in the same direction

as a meta-analysis that observed no increase in hypertensive disorders of pregnancy during the pandemic period compared with the prepandemic period (26).

*Strengths and weaknesses of our study*

One of the principal strengths of our study was our uniform COVID-19 screening strategy, targeted according to maternal symptoms: only patients with symptoms suggestive of COVID-19 infection were tested. As we have mentioned before, the performance of routine screening in a group of women among whom preeclampsia is over-represented, especially in cases of hospitalization, increases the likelihood of finding a positive test result in this group. Moreover, the selection of women from the prepandemic period in the unexposed group enabled us to be certain that they had not been exposed to this virus. We accordingly avoided the classification bias that would have led to the erroneous inclusion in the unexposed group of asymptomatic women with COVID-19 infection.

On the other hand, our study collected the data necessary to determine the relative chronology between the COVID-19 infection and preeclampsia: this viral infection preceded the preeclampsia in three women in our study in whom this association was observed. In the studies thus far published, no study specifies the chronology of these two diseases, a lacuna that limits their validity.

Our study used the standard French definition of preeclampsia. This strict definition allowed us to limit the probability of an erroneous diagnosis of preeclampsia in women with non-specific clinical and laboratory signs that are also linked to infection by SARS-CoV-2.

Finally, we chose to exclude from our study in utero transfers from other maternity units. That is, preeclampsia is a frequent reason for transfers to our level 3 perinatal center. The potentially variable screening policy for COVID-19 among the centers transferring patients to our hospital might thus have increased the probability of finding an association between COVID-19 and preeclampsia.

Our study has several limitations. Its extrapolability may be questionable as it took place in a single center. On the other hand, this enabled us to provide homogeneous management and follow-up care to the women included. Moreover, the number of patients with preeclampsia in our study was small (N = 7), so we cannot exclude that the absence of difference between the two groups may be due to a low statistical power. Finally, the number of nulliparas was lower in the group exposed to COVID-19, while nulliparity is a factor recognized to be associated with preeclampsia. One hypothesis that might explain this difference is that the nulliparas followed the preventive public health measures during the COVID-19 epidemic better while the parous women might have been contaminated by their children. The sensitivity study among the nulliparas as well as the multivariate analysis that adjusted for nulliparity found no significant association between preeclampsia and symptomatic COVID-19 infection. Nonetheless a lack of power cannot be ruled out, because preeclampsia was four times more frequent among the exposed than the unexposed nulliparas.

The choice to consider only the patients with symptomatic COVID-19 enabled us to have good exposure measurements; its limitation is that the interpretation of the association covers only symptomatic COVID-19 and preeclampsia, and not COVID-19 in the broader sense of the term, including asymptomatic infected women.

One hypothesis to explain an association between preeclampsia and COVID-19 appears to be the binding of SARS-CoV-2 to placental ACE2 receptors, leading to some placental lesions and possibly vascular diseases such as preeclampsia (13−15,27). Moreover, SARS-CoV-2 may be responsible for specific placental lesions known as placentitis, defined by the coexistent occurrence of 3 microscopic

findings: chronic histiocytic intervillositis, increased fibrin deposition, and trophoblast necrosis. Although rare, these lesions result in placental malperfusion and insufficiency and have proven to be clinically responsible for fetal growth restriction and perinatal death (28). We could hypothesize that these lesions could also be responsible for preeclampsia.

The pathogenesis of preeclampsia appears, nonetheless, to occur during the first trimester of pregnancy, at the moment of placentation. In our study and in most studies of the association between COVID-19 and preeclampsia, the patients included were infected during the second and third trimesters of pregnancy. One possible explanation is that some patients only started their follow-up at the hospital after the first trimester of pregnancy, and that they did not declare or were not diagnosed with an infection that could have occurred in early pregnancy. It would be interesting to study the impact of SARS-CoV-2 infection on the onset of pregnancy-related vascular diseases according to gestational age at infection, and especially during the first trimester of pregnancy.

## Conclusion

Symptomatic COVID-19 infection does not appear to increase the incidence of placental vascular disease, even though the size of our sample prevents us from reaching a definitive conclusion about whether a moderate or low risk exists. As of today, it does not appear necessary to reinforce obstetric surveillance for preeclampsia for women with symptomatic COVID-19 infection during pregnancy.

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