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RESEARCH ARTICLE

Impact of SARS-CoV-2 infection on risk of prematurity, birthweight and obstetric complications: A multivariate analysis from a nationwide, population-based retrospective cohort study

Emmanuel Simon[1] | **Jean-Bernard Gouyon**[2] | **Jonathan Cottenet**[3] | **Sonia Bechraoui-Quantin**[3] | **Patrick Rozenberg**[4] | **Anne-Sophie Mariet**[3,5,6] | **Catherine Quantin**[3,5,6,7]

[1]Gynaecology, Obstetrics, and Fetal Medicine, University Hospital, Dijon, France

[2]Centre d'Etudes Périnatales Océan Indien (EA 7388), Centre Hospitalier Universitaire Sud Réunion, La Réunion, Saint Pierre, France

[3]Biostatistics and Bioinformatics (DIM), University Hospital, Dijon, France

[4]Department of Obstetrics and Gynaecology, Hôpital Intercommunal de Poissy, Université Versailles Saint-Quentin, Poissy, France

[5]Inserm, CIC 1432, Dijon, France

[6]Clinical Investigation Centre, Clinical Epidemiology/Clinical Trials Unit, Dijon University Hospital, Dijon, France

[7]High-Dimensional Biostatistics for Drug Safety and Genomics, Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, CESP, Villejuif, France

Correspondence
Catherine Quantin, CHU de Dijon - Service de Biostatistique et d'Informatique Médicale - BP 77908, 21079 Dijon CEDEX, France.
Email: catherine.quantin@chu-dijon.fr

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Abstract

Objective: To determine the impact of maternal coronavirus disease 2019 (COVID-19) on prematurity, birthweight and obstetric complications.

Design: Nationwide, population-based retrospective cohort study.

Setting: National *Programme de Médicalisation des Systèmes d'Information* database in France.

Population: All single births from March to December 2020: 510 387 deliveries, including 2927 (0.6%) with confirmed COVID-19 in the mother and/or the newborn.

Methods: The group with COVID-19 was compared with the group without COVID-19 using the chi-square test or Fisher's exact test, and the Student's *t* test or Mann–Whitney *U* test. Logistic regressions were used to study the effect of COVID-19 on the risk of prematurity or macrosomia (birthweight ≥4500 g).

Main outcome measures: Prematurity less than 37, less than 28, 28–31, or 32–36 weeks of gestation; birthweight; obstetric complications.

Results: In singleton pregnancies, COVID-19 was associated with obstetric complications such as hypertension (2.8% versus 2.0%, $p < 0.01$), pre-eclampsia (3.6% versus 2.0%, $p < 0.01$), diabetes (18.8% versus 14.4%, $p < 0.01$) and caesarean delivery (26.8% versus 19.7%, $p < 0.01$). Among pregnant women with COVID-19, there was more prematurity between 28 and 31 weeks of gestation (1.3% versus 0.6%, $p < 0.01$) and between 32 and 36 weeks of gestation (7.7% versus 4.3%, $p < 0.01$), and more macrosomia (1.0% versus 0.7%, p = 0.04), but there was no difference in small-for-gestational-age newborns (6.3% versus 8.7%, $p = 0.15$). Logistic regression analysis for prematurity showed an adjusted odds ratio (aOR) of 1.77 (95% CI 1.55–2.01) for COVID-19. For macrosomia, COVID-19 resulted in non-significant aOR of 1.38 (95% CI 0.95–2.00).

Conclusions: COVID-19 is a risk factor for prematurity, even after adjustment for other risk factors.

KEYWORDS
COVID-19, hypertension, pre-eclampsia, prematurity, SARS-CoV-2, small for gestational age

Tweetable abstract: The risk of prematurity is twice as high in women with COVID-19 after adjustment for factors usually associated with prematurity.

1 | INTRODUCTION

The maternal and perinatal impact of the coronavirus disease 2019 (COVID-19) pandemic has already been the subject of numerous publications and meta-analyses. A recent meta-analysis, which identified 3592 citations and 40 studies,[1] found no change in the rate of prematurity before 37 weeks of gestation for the 15 studies considered.[2–26] However, there were significant disparities between high-income and low-income countries, with decreases in prematurity (12 studies) and in spontaneous prematurity (two studies) observed in high-income countries.[1] The interpretation of the results on prematurity remains difficult because, although there is a potential adverse effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, there are also the effects of health measures specific to each country on uninfected pregnant women. In addition, the epidemiology of COVID-19 fluctuated in the pregnant population over the various study periods and from one country to another, and the proportion of women who were infected at the beginning of the pandemic remains unclear. Only three national studies included in the meta-analysis (from the Netherlands, Denmark and Botswana) defined the risk of prematurity as their primary objective.[1,7,25,27] In the Netherlands, there was a decrease in prematurity less than 37 weeks of gestation after the introduction of health measures.[27] In Denmark, the decrease in prematurity was significant before 28 weeks of gestation, but not beyond.[7] In Botswana, the authors found a decrease in prematurity before 32 and 37 weeks of gestation.[25] These national studies focused more on the overall impact of the health measures (whether or not there was a lockdown) than on the complications of women with COVID-19. Furthermore, the authors did not perform modelling to avoid possible confounding biases. One multicentre cohort study that was published after the meta-analysis focused specifically on infected women; it reported an increased risk of prematurity, induced prematurity, severe infection, pre-eclampsia and eclampsia (706 women with COVID-19 versus 1424 without COVID-19).[28] These outcomes had already been suggested by previous studies and meta-analyses.[14,29–63]

Considering the small number of national or regional epidemiological studies in the most recent well-conducted reviews, we believe that a study characterising the perinatal impact of SARS-CoV-2 in all deliveries in France over a 1-year-period would be a valuable addition to the current literature. The first aim of our study was therefore to verify whether there was an increased risk of prematurity in women with COVID-19 and to compare this result with data on birthweight and obstetric complications. Second, we wanted to determine the specific influence of SARS-CoV-2 infection compared with other risk factors for prematurity using a multivariate analysis. This type of analysis has not yet been included in a comprehensive national study.

2 | METHODS

2.1 | Study design and participants

This retrospective cohort study was conducted using the national *Programme de Médicalisation des Systèmes d'Information* (PMSI) database.

The PMSI database provides detailed medical information on all admissions to public and private hospitals in France, including discharge diagnosis according to the tenth edition of the International Classification of Diseases (ICD-10) codes, medical procedures coded according to the French medical classification for clinical procedures (CCAM), and data related to pregnancy, such as gestational age. In France, almost all deliveries are recorded in the PMSI database because out-of-hospital delivery is rare, accounting for only 0.4% of births.[64]

We included all single births from March to December 2020 and for which the hospital stay ended before the end of 2020. Single births were identified through the linkage between newborn stays (including Z380 to Z382 ICD-10 codes) and maternal stays (ICD-10 codes Z370 or Z371 associated with a delivery procedure).

Using the data from the mother's delivery stay or on the newborn's birth stay, we defined two groups according to COVID-19 status. We searched the primary diagnoses, related diagnoses or associated diagnoses for the ICD-10 codes U0710, U0711, U0712, U0714 or U0715 (this algorithm has been used in previous studies[65–67]). If the newborn's birth stay and/or the mother's delivery stay included a code for COVID-19, they were considered as having COVID-19 (Group 1). If neither the newborn's birth stay nor the mother's delivery stay included a code for COVID-19, then they were considered as not having COVID-19 (Group 2).

The codes and headings are provided in Table S1.

2.2 | Variables

The following variables were extracted for each newborn stay: sex, gestational age, birthweight, malformations according to EUROCAT.[68]

Prematurity was defined according to the World Health Organization classification as a birth that occurred before 37 weeks of gestation.[69,70] We also considered extremely preterm births (before 28 weeks of gestation), moderate preterm births (between 28 and 31 weeks of gestation) and late preterm births (between 32 and 36 weeks of gestation). Induced prematurity was identified through ICD-10 codes linked to the aetiology for prematurity (Table S1).

We estimated small for gestational age (SGA) using the Ego growth curve,[71] and the Fenton growth curve was used for premature births.[72,73]

Finally, we were able to identify the age of the mother, the mode of delivery (vaginal delivery, caesarean) and maternal comorbidities: hypertensive disorders (pre-eclampsia and hypertension), retroplacental haematoma, diabetes (pre-existing and gestational diabetes), asthma and obesity (body mass index [BMI] ≥35 kg/m^2). Comorbidities were retrieved from the mother's delivery stay or another stay during pregnancy (ICD-10 and CCAM codes and headings are provided in Table S1). Similarly, details of non-COVID-19 infections (including chorioamnionitis, genitourinary infections and other infections possibly linked to preterm birth) were collected at delivery and during pregnancy, and we identified deliveries in the previous 10 years. Lastly, we collected data relative to admission to the intensive care unit and in-hospital maternal death up to 42 days after delivery.

2.3 | Statistical analysis

Qualitative variables were presented as frequencies (percentage). Quantitative variables were presented as means ± standard deviation and medians (interquartile range, Q1–Q3). The COVID-19 and non-COVID-19 groups were compared using the chi-square test or the Fisher's exact test (for qualitative variables) and Student's *t* test or Mann–Whitney *U* test (for quantitative variables) when applicable.

To study the effect of COVID-19 on the risk of prematurity or macrosomia (birthweight ≥4500 g), we performed logistic regressions adjusting for newborn sex, maternal age (≤18, 19–39 and ≥40 years), childbirth in the previous 10 years, retroplacental haematoma, diabetes (separated into pre-existing and gestational diabetes), hypertensive disorders (separated into pre-eclampsia and hypertension), obesity (BMI ≥35 kg/m^2) and malformations. Infections possibly linked to preterm birth were also added as an adjustment factor in a separate model. The variables included in the multivariate models were those significant in univariate with a *p* value less than 0.20 or judged useful according to the literature. Correlations were studied and interactions were tested. The results were reported as odds ratios (OR) and 95% CI.

We also performed a multimodal logistic regression to study the effect of COVID-19 on the risk of induced and spontaneous prematurity.

To take caesarean birth into account in the analysis of the risk of prematurity, we added caesarean delivery as an adjustment factor. However, due to interaction with several variables included in the initial regression, we performed specific regressions: one for caesarean deliveries and one for vaginal deliveries.

Various approaches to testing have been implemented in France since the beginning of the SARS-CoV-2 epidemic. In March 2020, only possible COVID-19 cases were tested; in May 2020 it became routine to ask patients whether they had any symptoms. From approximately October 2020, women were routinely tested in all French hospitals before caesarean section, before induction and even in spontaneous delivery, even if they were asymptomatic. We therefore performed sensitivity analyses by limiting the months of analysis from May to December and from October to December.

We performed another sensitivity analysis in women who gave birth in the previous 10 years to include previous preterm birth.

Finally, as a sensitivity analysis, we recovered information about COVID-19 infections during pregnancy and performed the same regressions to study the effect of COVID-19 on the risk of prematurity and macrosomia.

Statistical significance was set at *p* values less than 0.05. All analyses were performed using SAS software (SAS Institute Inc, Version 9.4, Cary, NC, USA).

2.4 | Role of the funding source

The project was funded by the French National Research Agency.

All authors had access to all the data reported in the study. The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

CQ and JC had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3 | RESULTS

Among the 510 387 singleton deliveries that occurred between March and December 2020, we identified 2927 cases of COVID-19 (0.6%) that were recorded on the mother's delivery or on the newborn's birth stay. Specifically, there were 2898 mothers with COVID-19 at delivery and 69 newborns with COVID-19 at birth (40 newborns with COVID-19 at birth had a mother with COVID-19 at delivery).

The two groups, COVID-19 infection versus no-COVID-19 infection, are described and compared in Table 1. Concerning maternal characteristics, the mean age of our study population was 31 years, and 53% of women had no childbirth in the previous 10 years, without significant differences between groups. Conversely, we found that the

TABLE 1 Characteristics of our study population and comparison between COVID-19 infection and non-COVID-19 infection (March–December 2020)

	Total	COVID-19 infection	Non-COVID-19 infection	
n	**510 387**	**2927**	**507 460**	***p* value**
Maternal variables				
Age (years)				
Mean ± SD	31 ± 5	30 ± 6	31 ± 5	0.9330
Median (IQR)	31 (27–34)	30 (26–34)	31 (27–34)	
Minimum–Maximum	12–56	13–49	12–56	
Mode of delivery, *n* (%)				
Caesarean	100 581 (19.7)	783 (26.8)	99 798 (19.7)	<0.01
Vaginal deliveries	409 806 (80.3)	2144 (73.3)	407 662 (80.3)	<0.01
No childbirth in the previous 10 years	274 031 (53.7)	1561 (53.3)	272 470 (53.7)	0.6954
Comorbidities, *n* (%)				
Hypertensive disorders	20 736 (4.1)	188 (6.4)	20 548 (4.1)	<0.01
Type of hypertensive disorders				
Pre-eclampsia	10 393 (2.0)	106 (3.6)	10 287 (2.0)	<0.01
Hypertension	10 343 (2.0)	82 (2.8)	10 261 (2.0)	0.0028
Retroplacental haematoma	1757 (0.3)	14 (0.5)	1743 (0.3)	0.2143
Diabetes	73 510 (14.4)	549 (18.8)	72 961 (14.4)	<0.01
Pre-existing diabetes	3882 (0.8)	51 (1.7)	3831 (0.8)	<0.01
Gestational diabetes	69 628 (13.6)	498 (17.0)	69 130 (13.6)	<0.01
Asthma	4173 (0.8)	39 (1.3)	4134 (0.8)	0.0019
Obesity (BMI ≥35 kg/m^2)	13 811 (2.7)	129 (4.4)	13 682 (2.7)	<0.01
Non-COVID-19 infections[a]	49 931 (9.8)	699 (23.9)	49 232 (9.7)	<0.01
Admission to ICU	838 (0.2)	80 (2.7)	758 (0.2)	<0.01
Hospital maternal death up to 42 days	25 (0.005)	1 (0.03)	24 (0.005)	0.13
Newborn variable, *n* (%)				
Sex (male)	260 590 (51.1)	1488 (50.8)	259 102 (51.1)	0.8110
Gestational age (weeks)				
Mean ± SD	39 ± 2	39 ± 2	39 ± 2	<0.01
Median (IQR)	39 (38–40)	39 (38–40)	39 (38–40)	
Minimum–Maximum	22–44	22–42	22–44	
Prematurity, *n* (%)	27 815 (5.5)	288 (9.8)	27 527 (5.4)	<0.01
Extreme (22–27 weeks)	3178 (0.6)	26 (0.9)	3152 (0.6)	0.0669
Moderate (28–31 weeks)	2832 (0.6)	37 (1.3)	2795 (0.6)	<0.01
Late (32–36 weeks)	21 805 (4.3)	225 (7.7)	21 580 (4.3)	<0.01
Birthweight (g)				
Mean ± SD	3279 ± 543	3226 ± 597	3279 ± 543	<0.01
Median (IQR)	3305 [3000–3615)	3260 (2950–3600)	3305 (3000–3615)	
Minimum–Maximum	100–7000	120–5120	100–7000	
<1500, *n* (%)	5816 (1.1)	56 (1.9)	5760 (1.1)	<0.01
1500–2499, *n* (%)	23 906 (4.7)	190 (6.5)	23 716 (4.7)	<0.01
≥2500, *n* (%)	480 665 (94.2)	2681 (91.6)	477 984 (94.2)	<0.01
≥4500, *n* (%)	3463 (0.7)	29 (1.0)	3434 (0.7)	0.0390

(Continues)

TABLE 1 (Continued)

	Total	COVID-19 infection	Non-COVID-19 infection	
n	510 387	2927	507 460	*p* value
Small for gestational age, *n* (%)				
Ego curve	54 587 (10.7)	319 (10.9)	54 268 (10.7)	0.7125
Fenton curve (among premature)	2406 (8.7)	18 (6.3)	2388 (8.7)	0.1453
Malformations according to EUROCAT	17 376 (3.4)	99 (3.4)	17 277 (3.4)	0.9471

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.
[a]Including chorioamnionitis, genitourinary infections and other infections possibly linked to preterm birth.

TABLE 2 Logistic regression to assess the risk of prematurity

	OR (95% CI)	*p* value	aOR (95% CI)	*p* value
COVID-19 infection	1.90 (1.68–2.15)	<0.01	1.77 (1.55–2.01)	<0.01
Male	1.12 (1.09–1.14)	<0.01	1.12 (1.10–1.15)	<0.01
Maternal age (years) (ref = 19–39 years)				
≤18	1.77 (1.60–1.96)	<0.01	1.69 (1.52–1.88)	<0.01
≥40	1.37 (1.30–1.44)	<0.01	1.20 (1.14–1.27)	<0.01
No childbirth in the previous 10 years	1.24 (1.21–1.27)	<0.01	1.16 (1.13–1.19)	<0.01
Retroplacental haematoma	22.01 (20.02–24.20)	<0.01	19.31 (17.45–21.36)	<0.01
Hypertensive disorders	5.58 (5.39–5.78)	<0.01	–	–
Type of hypertensive disorders				
Pre-eclampsia	10.68 (10.23–11.14)	<0.01	9.62 (9.20–10.06)	<0.01
Hypertension	1.92 (1.79–2.06)	<0.01	1.70 (1.59–1.83)	<0.01
Obesity (BMI ≥35 kg/m^2)	1.62 (1.53–1.73)	<0.01	1.16 (1.09–1.25)	<0.01
EUROCAT malformation	3.62 (3.47–3.78)	<0.01	3.62 (3.47–3.79)	<0.01
Overall diabetes	1.28 (1.24–1.33)	<0.01	–	–
Type of diabetes				
Pre-existing diabetes	3.87 (3.56–4.21)	<0.01	2.79 (2.54–3.06)	<0.01
Gestational diabetes	1.16 (1.12–1.20)	<0.01	1.06 (1.02–1.10)	<0.01

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, Odds ratio.

COVID-19 group was more likely to deliver by caesarean (26.8% versus 19.7%, $p < 0.01$), had more non-COVID-19 infections contracted during pregnancy or at delivery (23.9% versus 9.7%, $p < 0.01$), had more comorbidities, including hypertensive disorders (6.4% versus 4.1%, $p < 0.01$), diabetes (18.8% versus 14.4%, $p < 0.01$) and obesity (4.4% versus 2.7%, $p < 0.01$), and had more frequent intensive care unit admission (2.7% versus 0.2%, $p < 0.01$). It should be noted that we found no significant difference ($p = 0.13$) in the rate of in-hospital maternal death up to 42 days after delivery between women with and without COVID-19 infection.

Among newborns (Table 1), we found no difference in sex between groups (it should be noted that although the difference was not significant, there were more males among the 69 children affected by COVID-19). Prematurity was twice as frequent in the COVID-19 group than in the non-COVID-19 group (9.8% versus 5.4%, $p < 0.01$), in particular for moderate and late preterm births. Among preterm births, we also found significantly more induced prematurity in the COVID-19 group than in the non-COVID-19 group (50.7% versus 38.1%, $p < 0.01$). In the COVID-19 group, we found more newborns with a birthweight less than 2500 g (8.4% versus 5.8%, p <0.01) and also with a birthweight of 4500 g or more (1.0% versus 0.7%, $p < 0.01$). However, we found no differences between groups for SGA, whether using the Ego curve or the Fenton curve in preterm newborns, and there was no difference in malformations.

We then estimated the risk of prematurity or macrosomia (birthweight ≥4500 g) using logistic regressions. We found that COVID-19 was associated with prematurity (Table 2) in univariate and multivariate analyses, with an almost two-fold increase in risk (adjusted OR [aOR] = 1.77 95% CI 1.55–2.01), after adjustment for all variables cited above, in particular the factors usually associated with prematurity (extreme maternal ages, no childbirth in the previous 10 years, retroplacental haematoma, pre-eclampsia, hypertension, obesity, pre-existing diabetes, gestational diabetes and malformations). Adding non-COVID-19 infections as

TABLE 3 Logistic regression to assess the risk of macrosomia

	OR (95% CI)	*p* value		aOR (95% CI)	*p* value
COVID-19 infection	1.47 (1.01–2.12)	0.0402	COVID-19 infection	1.38 (0.95–2.00)	0.0873
Male	2.36 (2.19–2.54)	<0.01	Male	2.35 (2.18–2.53)	<0.01
Maternal age (years) (ref = 19–39 years)			Maternal age (years) (ref = 19–39 years)		
≤18	0.37 (0.21–0.66)	0.0007	≤18	0.50 (0.28–0.88)	0.0163
≥40	1.12 (0.97–1.30)	0.1306	≥40	1.04 (0.89–1.21)	0.6229
No childbirth in the previous 10 years	0.57 (0.53–0.61)	<0.01	No childbirth in the previous 10 years	0.59 (0.55–0.63)	<0.01
Retroplacental haematoma	0.50 (0.23–1.12)	0.0911	Retroplacental haematoma	0.50 (0.23–1.13)	0.0945
Hypertensive disorders	0.80 (0.66–0.96)	0.0171	Hypertensive disorders	–	–
Type of hypertensive disorders			Type of hypertensive disorders		
Pre-eclampsia	0.66 (0.49–0.88)	0.0047	Pre-eclampsia	0.58 (0.44–0.78)	0.0003
Hypertension	0.93 (0.73–1.19)	0.5738	Hypertension	0.76 (0.60–0.98)	0.0320
Obesity (BMI ≥35 kg/m^2)	2.52 (2.20–2.89)	<0.01	Obesity (BMI ≥35 kg/m^2)	–	–
EUROCAT malformation	0.94 (0.78–1.14)	0.5167	EUROCAT malformation	–	–
Overall diabetes	1.70 (1.57–1.84)	<0.01	Overall diabetes	–	–
Type of diabetes			Type of diabetes for women with obesity (BMI ≥35 kg/m^2)		
Pre-existing diabetes	5.98 (5.03–7.11)	<0.01	Pre-existing diabetes	3.25 (2.07–5.08)	<0.01
Gestational diabetes	1.47 (1.34–1.60)	<0.01	Gestational diabetes	1.36 (1.03–1.80)	0.0287
			Type of diabetes for women without obesity		
			Pre-existing diabetes	6.08 (5.01–7.38)	<0.01
			Gestational diabetes	1.34 (1.22–1.48)	<0.01

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, Odds ratio.

another adjustment factor, we found similar results and the significant effect of COVID-19 was maintained (aOR = 1.61, 95% CI 1.42–1.84, Table S2). Separating the analyses according to the type of delivery (caesarean or vaginal), COVID-19 infection was still associated with prematurity whatever the mode of delivery (aOR = 2.38, 95% CI 1.96–2.88 and aOR = 1.32, 95% CI 1.10–1.59, respectively; Table S3). When we separated prematurity into spontaneous and induced, we found that COVID-19 was associated with both types of prematurity (aOR = 1.45, 95% CI 1.22–1.72 and aOR = 2.27, 95% CI 1.90–2.71, respectively; Table S4).

In women who had given birth in the previous 10 years, the effect of the COVID-19 infection persisted in the risk of prematurity (aOR = 2.49, 95% CI 2.08–2.99, Table S5).

Having COVID-19 was significantly associated with macrosomia in univariate analysis (OR = 1.47, 95% CI 1.01–2.12) (Table 3). However, the association was no longer significant in multivariate analysis (aOR = 1.38, 95% CI 0.95–2.00) after adjustment and taking into account a significant interaction found between obesity and diabetes, particularly pre-existing diabetes. The main factor associated with macrosomia was diabetes, with a similar effect for gestational diabetes with or without obesity (aOR = 1.36, 95% CI 1.03–1.80 and aOR = 1.34, 95% CI 1.22–1.48, respectively), and a very strong effect of pre-existing diabetes, with twice the risk for women without obesity (aOR = 6.08, 95% CI 5.01–7.38) compared to those with obesity (aOR = 3.25, 95% CI 2.07–5.08). Pre-eclampsia, maternal age less than 18 years and not having had children in the previous 10 years were protective factors for macrosomia.

When we limited the analysis to May–December and October–December, the results showed a significant effect of COVID-19 on prematurity (aOR = 1.57, 95% CI 1.35–1.82 and aOR = 1.47, 95% CI 1.21–1.78, respectively, Table S6), similar to the initial analyses, and a non-significant effect in the risk of macrosomia (with an adjusted OR still greater than 1, around 1.30 but not significant, Table S7). It should be noted that when we compared the number of COVID-19 cases at delivery or birth per month and the number of hospitalised patients with COVID-19, the two curves were comparable from the month of May, with a similar increase in the month of October (Figure S1).

Finally, including women diagnosed with COVID-19 during pregnancy, we found a rate of 0.8% of COVID-19 (n = 3916 instead of n = 2927). We performed the analyses including these 3916 cases of COVID-19 and still found that COVID-19 had a significant effect on the risk of prematurity (aOR = 1.65, 95% CI 1.47–1.85, Table S8) and a non-significant effect in the risk of macrosomia (with aOR still greater than 1, around 1.30 but not significant).

4 | DISCUSSION

4.1 | Main findings

Our study confirms that SARS-CoV-2 infection is a risk factor for moderate and late prematurity in singleton pregnancies. In the COVID-19 group, there was more maternal

obesity (BMI ≥35 kg/m^2) and more complications, including hypertension, pre-eclampsia, diabetes and caesarean section. There were also more infants with birthweights below 1500 g and below 2500 g, but not more SGA newborns.

Having COVID-19 multiplies the risk of prematurity by 1.77 overall (2.25 for induced prematurity and 1.45 for spontaneous prematurity) after adjustment and independent of the other classic risk factors that were found to be significantly associated with prematurity: retroplacental haematoma, pre-eclampsia, EUROCAT congenital malformations, pre-gestational diabetes, hypertension without pre-eclampsia, young maternal age (<18 years), obesity (≥35 kg/m^2), predominance of girls, and other infections (including chorioamnionitis and genitourinary infections). In this logistic regression, the adjusted odds ratio associated with COVID-19 was higher than that of gestational hypertension, age, absence of childbirth in the preceding 10 years, BMI ≥35 kg/m^2, sex of the newborn or gestational diabetes. In contrast, this adjusted odds ratio was lower than the adjusted odds ratio for retroplacental haematoma, pre-eclampsia or eclampsia, malformations and pre-existing diabetes. This excess in risk associated with COVID-19 is significant both in case of a caesarean delivery (aOR = 2.38) and of vaginal delivery (aOR = 1.32). When we considered a possible previous delivery within 10 years, we found that this excess in risk associated with COVID-19 was still significant, but was higher for women with a previous delivery within 10 years (aOR = 2.49) than for women without (aOR = 1.33).

In the univariate analysis, there was a higher likelihood of birthweight of 4500 g or more in the presence of COVID-19. However, this difference was not apparent in the logistic model evaluating macrosomia after adjustment for other risk factors.

4.2 | Strengths and limitations

The main strength of our study is the use of comprehensive nationwide PMSI data. The fact that these national data are used for the allocation of hospital budgets encourages improvement in data quality in terms of coherence, accuracy and exhaustiveness, and justifies its use in several domains including perinatality.[74–76] A previous validation study[77] confirmed the quality and the exhaustiveness of PMSI data, especially for the recording of gestational age. These data are also a valuable resource for the evaluation of perinatal care and management because the PMSI database allows the linkage of consecutive hospital discharge abstracts and, for singleton pregnancy, mothers' and children's abstracts have been linked by a shared anonymous key since 2012.

In our study, exposure to COVID-19 occurred at the end of pregnancy: exposure was relatively homogeneous in our population, unlike in some studies in which infection occurred at different gestational ages.[28] Moreover, the diagnosis was systematically validated by means of a real-time polymerase chain reaction (PCR). Another distinct advantage is that our population is representative of all women giving birth in France because only 0.4% of women give birth outside the hospital setting in France.[64] International multicentre studies are not able to obtain such a high level of representativeness for the participating countries. We were therefore able to avoid the selection bias of certain studies conducted in university centres, in which there is a disproportionate rate of women at risk.

Moreover, COVID-19 vaccination was not authorised for pregnant women in France during the period studied, which had the advantage of not constituting an additional bias.

We recognise that there are also several limitations to this study. First, our use of a hospital medical-administrative database results in a lack of potentially explanatory and sufficiently reliable data, and we do not have systematic access to certain variables of interest such as diet, smoking and thromboembolic events that may have occurred during pregnancy. Concerning non-COVID-19 infections, we took into account infections such as chorioamnionitis, genitourinary infections and other infections possibly linked to preterm birth that were recorded during any hospital stay that occurred during pregnancy or delivery. However, we were not able to identify all infections that occurred during the pregnancy. Similarly, parity could not be taken into account directly, but only with the pregnancies that had occurred in the previous 10 years. Unfortunately, in our national database, we do not have information on glycaemic control in women with diabetes. We were nevertheless able to identify gestational and pre-existing diabetes separately, and to take the two conditions into account as adjustment factors.

COVID-19 status was only attributed if the woman or newborn was diagnosed during the hospital stay, and COVID-19 during pregnancy was not taken into account. This definition allowed us to limit the heterogeneity of exposure to COVID-19 in terms of gestational age, as observed in many other studies. Nevertheless, even considering COVID-19 during pregnancy, we found similar results on the risk of prematurity or macrosomia. While all COVID-19 diagnoses were biologically confirmed with a mandatory PCR test and medically validated, diagnostic testing was limited at the beginning of the pandemic, so women and newborns in the non-COVID-19 group may in fact have had the infection but were just not tested. However, having 'cases' (more exactly exposed) within a 'control' (more exactly non-exposed) population should move results towards the null (rather than away from it). Our analysis may therefore have underestimated the effects of COVID-19 infection. This suggests that the findings of increased prematurity are a conservative estimate.

4.3 | Interpretation

The fact that COVID-19 is a risk factor for prematurity has already been reported,[29] but our national study uses adjusted odds ratios to measure the influence of COVID-19 among other risk factors for prematurity. The effect also remained significant when we limited our analysis to the period when

COVID-19 tests were conducted more systematically or when we added COVID-19 occurring during pregnancy. We observed no association between COVID-19 and SGA neonates, which is an important finding. Our results on gestational age at delivery and birthweights were consistent. Our study obviously does not establish a pathophysiological mechanism for increased prematurity in COVID-19, but the absence of more SGA neonates suggests that the hypothesis of a direct placental vascular effect is unlikely.

The mechanism underlying excess prematurity is not the focus of this study. However, triggering of preterm delivery by a viral cause has been widely recognised for other viruses (chikungunya, dengue, Zika viruses). Transmission by blood outside the placental inflammation remains possible, as does postnatal transmission. A recent review of 20 studies by Sharps et al.[78] highlighted that if delivery occurs in the third trimester after maternal SARS-CoV-2 infection, placentas show fetal (35.3% of cases) and maternal (46%) vascular malperfusion and signs of inflammation (villitis 8.7% of cases, intervillositis 5.3% of cases, chorioamnionitis 6% of cases). Of those tested, a minority of neonates (2%) and placental specimens were positive for SARS-CoV-2 infection (21%). Data from Debelenko et al.[79] confirmed placental vascular malperfusion in a group of SARS-CoV-2 infections and found a correlation between the histopathological features and intrauterine growth restriction.

Therefore, the low rate of SGA neonates born to SARS-CoV-2-infected mothers in this study is unexpected regardless of the gestational age of the patients. However, a prospective cohort study in Teheran (Iran)[63] found no differences between neonates born to COVID-19-infected and uninfected mothers; not for intrauterine growth restriction (adjusted risk ratio: 0.16, 95% CI 0.02–1.86, $p = 0.145$), prematurity rate or any other neonatal conditions. There is a need for larger studies that include placental analyses and further investigations into the effects of COVID-19 according to gestational age.

Although the multivariate analysis was not significant, as expected, our results suggest that there is a potential association between COVID-19 and macrosomia. Furthermore, our data on diabetes and obesity seemed consistent, which reinforces the validity of our analysis: we found a higher risk of macrosomia in pre-existing diabetes than in gestational diabetes. In addition, the risk of macrosomia in pre-existing diabetes without obesity was higher than in pre-existing diabetes with obesity. In the first group, there were probably more women with diabetes on insulin, and more with type 2 diabetes in the second group. These findings appear to be consistent with the literature.[80]

This study did not identify an increased risk of congenital malformations in the infected group. However, the COVID-19 infections occurred late in pregnancy, whereas fetal malformations are mostly associated with early viral infections (e.g. rubella, cytomegalovirus).[81] Only a prospective study with antenatal diagnosis of malformations, identification of fetal deaths, neonatal diagnosis and follow up of potentially exposed newborns would allow a significant answer.

Considering the strongly suspected benefits of lockdown,[1] our results must be interpreted in view of the measures taken in France to mitigate the spread of COVID-19 during the study period. The first lockdown was imposed from 17 March 2020 to 11 May 2020, and the second, less strict, lockdown was from 30 October to 15 December 2020. If COVID-19 has an adverse effect on pregnancy, and the effect of lockdown is beneficial, it can be hypothesised that the effects vary according to the gestational age at time of exposure. This is a potential topic for future research.

Finally, our study did not allow us to establish the role of the different SARS-CoV-2 variants in prematurity. This subject also warrants future research.

5 | CONCLUSIONS

Infection with SARS-CoV-2 in singleton pregnancies was associated with obstetric complications such as hypertension, pre-eclampsia, diabetes and caesarean delivery, and pregnant women with COVID-19 were more likely to give birth between 28 and 31 weeks of gestation and between 32 and 36 weeks of gestation. However, we found no association between COVID-19 and SGA. Overall, COVID-19 status was a stronger risk factor for prematurity than hypertension, age, absence of a delivery in the preceding 10 years, BMI ≥35 kg/m^2, male sex of the newborn and gestational diabetes.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting Information.

AUTHOR CONTRIBUTION

ES, JBG and CQ were involved in the conception and design of the study. CQ was the coordinator of the study. JC, ASM and CQ were responsible for the data collection. ES, JC, JBG and CQ wrote the first draft. JC was in charge of the analysis. JC and CQ accessed and verified the data. ES, JC, ASM, SB-Q, PR, JBG and CQ were involved in the interpretation, critically reviewed the first draft and approved the final version.

ETHICAL APPROVAL

This study was approved by the Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé (CESREES, Ethics and Scientific Committee for Research, Studies and Evaluation in Health, 9 June 2020) and the Institut des Données de Santé (INDS, French Institute of Health Data, registration number 1611357, 15 June 2020) and authorised by the Commission

Nationale de l'Informatique et des Libertés (CNIL, French Data Protection Authority, registration number DR-2020-250, 3 July 2020).

DATA AVAILABILITY STATEMENT

The use of these data by our department was approved by the National Committee for data protection. We are not allowed to transmit these data. PMSI data are available for researchers who meet the criteria for access to these French confidential data (this access is submitted to the approval of the National Committee for data protection) from the national agency for the management of hospitalization (ATIH - Agence technique de l'information sur l'hospitalisation).

ORCID

Emmanuel Simon https://orcid.org/0000-0001-6442-1013
Catherine Quantin https://orcid.org/0000-0001-5134-9411

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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