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Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection

The WAPM (World Association of Perinatal Medicine) Working Group on COVID-19#

KEYWORDS: coronavirus; COVID-19; infection; pregnancy; SARS-CoV-2

CONTRIBUTION

What are the novel findings of this work?
In pregnancies complicated by SARS-CoV-2 infection, the risk of maternal mortality was 0.8%, but about 11% of women required admission to the intensive care unit. Pregnancies affected by SARS-CoV-2 infection were also complicated by preterm birth in 26.3% and perinatal death in 4.1% of cases. The risk of vertical transmission was negligible.

What are the clinical implications of this work?
Based on the results of our cohort, pregnant women infected with SARS-CoV-2 might be exposed to a higher risk of respiratory morbidity, while the risk of vertical transmission seems to be extremely low.

ABSTRACT

Objectives *To evaluate the maternal and perinatal outcomes of pregnancies affected by SARS-CoV-2 infection.*

Methods *This was a multinational retrospective cohort study including women with a singleton pregnancy and laboratory-confirmed SARS-CoV-2 infection, conducted in 72 centers in 22 different countries in Europe, the USA, South America, Asia and Australia, between 1 February 2020 and 30 April 2020. Confirmed SARS-CoV-2 infection was defined as a positive result on real-time reverse-transcription polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab specimens. The primary outcome was a composite measure of maternal mortality and morbidity, including admission to the intensive care unit (ICU), use of mechanical ventilation or death.*

Results *In total, 388 women with a singleton pregnancy tested positive for SARS-CoV-2 on RT-PCR of a nasopharyngeal swab and were included in the study. Composite adverse maternal outcome was observed in 47/388 women (12.1%); 43 women (11.1%) were admitted to the ICU, 36 (9.3%) required mechanical ventilation and three (0.8%) died. Of the 388 women included in the study, 122 (31.4%) were still pregnant at the time of data analysis. Among the other 266 women, six (19.4% of the 31 women with first-trimester infection) had miscarriage, three (1.1%) had termination of pregnancy, six (2.3%) had stillbirth and 251 (94.4%) delivered a liveborn infant. The rate of preterm birth before 37 weeks' gestation was 26.3% (70/266). Of the 251 liveborn infants, 69/251 (27.5%) were admitted to the neonatal ICU, and there were five (2.0%) neonatal deaths. The overall rate of perinatal death was 4.1% (11/266). Only one (1/251, 0.4%) infant, born to a mother who tested positive during the third trimester, was found to be positive for SARS-CoV-2 on RT-PCR.*

Conclusions *SARS-CoV-2 infection in pregnant women is associated with a 0.8% rate of maternal mortality, but an 11.1% rate of admission to the ICU. The risk of vertical transmission seems to be negligible.* © *2020 International Society of Ultrasound in Obstetrics and Gynecology*

INTRODUCTION

In December 2019, a novel coronavirus spread in China. Responsible for a cluster of respiratory disorders called COVID-19, it was identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1].

Coronaviruses are enveloped, non-segmented positive-sense RNA viruses belonging to the Nidovirales order[2]. Although responsible for generally mild infections, including many common colds in adults and children, coronaviruses have caused two important epidemics in the last decade: severe acute respiratory syndrome and Middle East respiratory syndrome, also known as SARS and MERS, respectively. Despite the large and rapidly growing number of cases worldwide[3], there are limited

Correspondence to: Dr D. Di Mascio, Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Via del Policlinico, 155. 00161 Rome, Italy (e-mail: dani.dimascio@gmail.com)

#Participants of WAPM Working Group are listed at end of article.

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data on COVID-19 in pregnancy, coming mainly from case series and small studies[4–7]. Pregnant women are at increased risk for severe illness from influenza viruses and other respiratory infections owing to cardiopulmonary adaptive changes, such as increased heart rate and stroke volume and reduced pulmonary residual capacity, that occur during pregnancy and that can increase the risk of hypoxemia and contribute to the increased severity. There is therefore concern that the course of COVID-19 in pregnant women may be associated with a higher burden of maternal mortality and morbidity compared with the general population.

A recent systematic review including all published reports on coronaviruses (COVID-19, SARS and MERS) in pregnancy found that preterm birth was the most common adverse pregnancy outcome, and that COVID-19 was associated with an increased risk of pre-eclampsia and Cesarean delivery[5,8–10]. Despite this, the small sample size, the inclusion of cases referred mainly for severe acute respiratory symptoms, lack of information on pre-existing medical conditions complicating pregnancy, and heterogeneity in gestational age at infection and outcomes observed, do not allow extrapolation of any objective evidence on the course of infection during pregnancy. The primary aim of this study was to evaluate the maternal and perinatal outcomes of pregnancies affected by SARS-CoV-2 infection.

METHODS

Study design and participants

This multinational, retrospective cohort study included all pregnant women with laboratory-confirmed SARS-CoV-2 infection diagnosed between 1 February 2020 and 30 April 2020 in 72 centers in 22 different countries (Argentina, Australia, Belgium, Brazil, Colombia, Czech Republic, Finland, Germany, Greece, Israel, Italy, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey and the USA) (Appendix S1). Women were included if they were diagnosed with SARS-CoV-2 infection antepartum during pregnancy, while those who tested positive only before conception or during the postpartum period were excluded from the study.

SARS-CoV-2 was diagnosed based on The World Health Organization (WHO) interim guidance[11]. A confirmed case of SARS-CoV-2 was defined as a positive result on real-time reverse-transcription polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab specimens[12,13]. In the included centers, women were tested with RT-PCR assay of nasopharyngeal swabs, mostly because of symptoms of, or exposure to, the virus at the time of triage. Neonates of women who were positive for SARS-CoV-2 were usually tested with RT-PCR assay of a nasopharyngeal swab within 24 h after delivery.

Data on recent SARS-CoV-2 exposure history, clinical symptoms or signs, laboratory findings and maternal and perinatal outcomes were collected. All medical records were anonymized and sent to the coordinating center at the University of Naples Federico II, Naples, Italy, through The World Association of Perinatal Medicine data platform or via an encrypted Research Electronic Data Capture (REDCap) data management platform. Data were entered into a computerized database and cross-checked. In cases of missing data, requests for clarification were sent to the coordinator at each participating center.

Ethical approval for the study was obtained from the Ethical Committee of Federico II University of Naples (nr. 145/2020).

Outcomes

The primary outcome of the study was a composite measure of maternal mortality and morbidity, termed 'composite adverse maternal outcome', including at least one of the following: admission to the intensive care unit (ICU), use of mechanical ventilation or death. Secondary outcomes were miscarriage, stillbirth, neonatal death, perinatal death, small-for-gestational age (SGA), preterm birth, Cesarean delivery, low birth weight, admission to the neonatal ICU (NICU), and vertical transmission confirmed by a positive RT-PCR assay in the neonate.

Miscarriage was defined as pregnancy loss before 22 weeks' gestation and stillbirth as intrauterine death at or after 22 weeks. Neonatal death was defined as death of a liveborn infant within the first 28 days postpartum, and perinatal death as either stillbirth or neonatal death. SGA was defined as ultrasound estimated fetal weight less than the 10th percentile[14]. Preterm birth was defined as delivery before 37 completed weeks of gestation and low birth weight as birth weight less than 2500 g. Fever was defined as an axillary temperature of 37.5°C or higher. Lymphocytopenia was defined as a lymphocyte count of less than 1500 cells/mm^3 and thrombocytopenia as a platelet count of less than 150 000/mm^3. Increased lactate dehydrogenase (LDH) level was defined as LDH level higher than 443 U/L in the first trimester, 447 U/L in the second trimester and 524 U/L in the third trimester of pregnancy. A computed tomography (CT) scan was performed at the physicians' discretion. CT abnormalities related to SARS-CoV-2 included 'ground-glass' opacity with or without consolidation or visible intralobular lines. Acute respiratory distress syndrome (ARDS) was defined in accordance with the WHO interim guidance[11].

Common criteria for admission to the ICU included all respiratory arrests, respiratory rate ≥ 40 or ≤ 8 breaths/min, oxygen saturation $< 90\%$ on $\geq 50\%$ oxygen, all cardiac arrests, pulse rate < 40 or > 140 beats/min, systolic blood pressure < 90 mmHg, sudden fall in level of consciousness (fall in Glasgow coma score of more than 2 points), repeat or prolonged seizures, rising arterial carbon dioxide tension with respiratory acidosis and any patient giving cause for concern.

Common reasons for admission to the NICU were prematurity, respiratory distress syndrome, sepsis, hypoglycemia and maternal chorioamnionitis.

Primary and secondary outcomes were evaluated in the overall cohort and separately in symptomatic and asymptomatic women. *Post-hoc* subgroup analysis according to region (European *vs* non-European countries; high-income *vs* middle-income countries) was performed for composite adverse maternal outcome, admission to the ICU, admission to the NICU and Cesarean delivery.

Statistical analysis

Statistical analysis was performed using SPSS v. 19.0 (IBM Inc., Armonk, NY, USA) and Stata version 13.1 (StataCorp., College Station, TX, USA, 2014). Continuous variables are reported as mean ± SD, while categorical variables are reported as *n* (%). Univariate comparisons of dichotomous data were performed using the χ-square test with continuity correction. Comparisons between groups were performed using Student's *t*-test to test group means by assuming equal within-group variances for parametric data, and the Wilcoxon and Mann–Whitney *U*-tests for non-parametric data. Multivariate analysis was performed to evaluate potential predictors of composite adverse maternal outcome. The final model was fitted using a stepwise forward process and including only covariates with an adjusted $P < 0.10$, with the exception of maternal age and pharmacological treatment, which were included *a priori*. The results of logistic regression analysis are reported as odds ratios (ORs) and adjusted ORs (aORs) with 95% CIs; $P < 0.05$ was considered statistically significant.

A standard diagnostic procedure was adopted to check the validity of the final models: the C statistic (area under the receiver-operating-characteristics curve).

Women were followed up from enrollment until 28 days postpartum or until the end date of the study, whichever came first. For composite adverse maternal outcome, the data of all enrolled women were analyzed. For multivariate analysis, only women with pregnancy completed by the study end date were included. Neonatal death was analyzed only for liveborn infants with 28 days of follow-up data.

RESULTS

Characteristics of included women

During the study period, 388 women with a singleton pregnancy who were positive for SARS-CoV-2 on RT-PCR of a nasopharyngeal swab, from 72 centers in 22 different countries, were included in the study.

Mean gestational age at diagnosis was 30.6 ± 9.5 weeks, with 8.0% (31/388) of women being diagnosed in the first, 22.2% (86/388) in the second and 69.8% (271/388) in the third trimester of pregnancy (Table 1). The most common symptom at the time of triage was a cough (52.1%), followed by fever (44.1%) and shortness of breath (15.5%), while 24.2% of women were asymptomatic. Chest CT was performed in 56/388 (14.4%) women, of whom 45/56 (80.4%) presented with bilateral multifocal involvement.

The most common pharmacologic therapy was hydroxychloroquine, used in 90 (23.2%) women. Antiviral drugs were used in 72 (18.6%) women, a combination of lopinavir and ritonavir being the most commonly used antiviral treatment (60/388 (15.5%)) (Table 1). There were no variations in drug use according to country.

Maternal outcome

Composite adverse maternal outcome was reported in 47/388 (12.1%) women, with 43/388 (11.1%) admitted

Table 1 Characteristics of 388 pregnant women with SARS-CoV-2 infection

Characteristic	*Value*
Living in high-income country	337 (86.9)
Living in European country	295 (76.0)
Healthcare worker	28 (7.2)
Smoker	54 (13.9)
Pre-existing chronic disease*	156 (40.2)
Obese†	28 (7.2)
Gestational age at infection (weeks)	30.6 ± 9.5
Trimester in which diagnosis made	
First	31 (8.0)
Second	86 (22.2)
Third	271 (69.8)
Chest CT scan	56 (14.4)
Bilateral CT abnormalities	45/56 (80.4)
Maternal age (years)	32.2 ± 6.1
COVID-19 symptoms at diagnosis	
Fever	171 (44.1)
Cough	202 (52.1)
Rhinorrhea	29 (7.5)
Myalgia	56 (14.4)
Anosmia	21 (5.4)
Shortness of breath	60 (15.5)
Diarrhea	16 (4.1)
Conjunctivitis	9 (2.3)
Any symptom	294 (75.8)
Laboratory findings	
Lymphocytopenia	156 (40.2)
Thrombocytopenia	40 (10.3)
Increased LDH levels	32 (8.2)
Pharmacologic treatment	
No specific pharmacologic treatment	222 (57.2)
Hydroxychloroquine	90 (23.2)
Any antibiotic	79 (20.4)
Azithromycin	58 (14.9)
Low-molecular-weight heparin	87 (22.4)
Antiviral drug	
Any antiviral drug	72 (18.6)
Darunavir/cobicistat	4 (1.0)
Oseltamivir	2 (0.5)
Lopinavir/ritonavir	60 (15.5)
Darunavir/ritonavir	2 (0.5)
Remdesivir	2 (0.5)

Data are given as *n* (%), *n*/*N* (%) or mean ± SD. *Including diabetes, hypertension or asthma. †Defined as body mass index ≥ 30 kg/m^2. CT, computed tomography; LDH, lactate dehydrogenase.

to the ICU and 36/388 (9.3%) requiring mechanical ventilation. There were 3/388 cases of maternal death, accounting for a maternal mortality rate of 0.8% (Table 2). One death occurred in a 33-year-old woman with Type-II diabetes mellitus. She presented at 33 weeks' gestation with stillbirth and was febrile and unconscious. Chest radiography showed pulmonary infiltrates and atelectasis with elevated left hemidiaphragm. The woman was admitted to the ICU and intubated but died with acute kidney injury and cardiac arrest. The second death occurred in a 27-year-old woman who presented at 34 weeks with severe shortness of breath. She underwent emergency Cesarean delivery and received continuous positive airway pressure ventilation but died of respiratory failure before intubation. The third death occurred in a 31-year-old woman who presented at 38 weeks with myalgia, fatigue, sore throat and severe hypertension. She underwent emergency Cesarean delivery owing to the uncontrolled high blood pressure and developed severe pre-eclampsia. After delivery, the woman was admitted to the ICU and received extracorporeal membrane oxygenation for acute respiratory failure complicated by pneumothorax and left lung hemorrhage and died 8 days after delivery. Details of women admitted to the ICU are shown in Table S1.

Perinatal outcome

Of the 388 women included in the study, 122 (31.4%) were still pregnant at the time of data analysis. Of the other 266 women, three (1.1%) had termination of pregnancy, six (2.3%) had stillbirth, six had miscarriage (19.4% of the 31 women with first-trimester infection) and 251 (94.4%) delivered a liveborn infant (Table 2, Figure 1). The most common mode of delivery was Cesarean section, performed in 136/251 (54.2%) women. Preterm birth before 37 weeks occurred in 70/266 women (26.3%), of which 56/70 (80.0%) were indicated and 14/70 (20.0%) were spontaneous.

Of the 251 liveborn infants, 69 (27.5%) were admitted to the NICU. There were 5/251 (2.0%) cases of neonatal death, of which three were born preterm and the other two died after developing late-onset sepsis. Only one (0.4%) of the 251 liveborn neonates was found to be positive for SARS-CoV-2 on RT-PCR of nasopharyngeal swabs performed after delivery. The mother had tested positive during the third trimester of pregnancy.

In the 266 women with a completed pregnancy, the overall number of perinatal deaths was 11 (4.1%). Among these cases, 10 women had COVID-19 symptoms at presentation and one was asymptomatic.

Table 2 Maternal and perinatal outcomes of 388 pregnancies with SARS-CoV-2 infection, overall and according to presence of symptoms at diagnosis

Outcome	*Total sample* (n = *388*)	*Symptomatic* (n = *294*)	*Asymptomatic* (n = *94*)	P
Maternal outcome				
Composite adverse maternal outcome*	47 (12.1 (9.2–15.7))	45 (15.3 (11.6–19.9))	2 (2.1 (0.6–7.4))	0.001
Admission to ICU	43 (11.1 (8.3–14.6))	42 (14.3 (10.8–18.8))	1 (1.1 (0.2–5.8))	< 0.001
Any type of mechanical ventilation	36 (9.3 (6.8–12.6))	35 (11.9 (8.7–16.1))	1 (1.1 (0.2–5.8))	0.002
Intubation	25 (6.4 (4.4–9.3))	25 (8.5 (5.8–12.3))	0 (0.0 (0.0–3.9))	0.003
ARDS	7 (1.8 (0.9–3.7))	7 (2.4 (1.2–4.8))	0 (0.0 (0.0–3.9))	0.13
ECMO	2 (0.5 (0.1–1.9))	2 (0.7 (0.2–2.5))	0 (0.0 (0.0–3.9))	0.4
Maternal death	3 (0.8 (0.3–2.2))	3 (1.0 (0.4–3.0))	0 (0.0 (0.0–3.9))	0.3
Ongoing pregnancy	122 (31.4 (27.0–36.2))	105 (35.7 (30.5–41.3))	17 (18.1 (11.6–27.1))	0.001
Completed pregnancy	266 (68.6 (63.8–73.0))	189 (64.3 (58.7–69.6))	77 (81.9 (72.9–88.4))	0.001
Perinatal outcome				
Completed pregnancies				
Termination of pregnancy	3/266 (1.1 (0.4–3.3))	2/189 (1.1 (0.3–3.8))	1/77 (1.3 (0.2–7.0))	0.9
Miscarriage†	6/31 (19.4 (9.2–36.3))	5/23 (21.7 (9.7–41.9))	1/8 (12.5 (2.2–47.1))	0.7
Stillbirth	6/266 (2.3 (1.0–4.8))	5/189 (2.6 (1.1–6.1))	1/77 (1.3 (0.2–7.0))	0.8
Perinatal death	11/266 (4.1 (2.3–7.3))	10/189 (5.3 (2.9–9.5))	1/77 (1.3 (0.2–7.0))	0.14
SGA	10/266 (3.8 (2.1–6.8))	9/189 (4.8 (2.5–8.8))	1/77 (1.3 (0.2–7.0))	0.2
Preterm birth	70/266 (26.3 (21.4–31.9))	60/189 (31.7 (25.5–38.7))	10/77 (13.0 (7.2–22.3))	0.002
Liveborn infant	251/266 (94.4 (90.9–96.6))	177/189 (93.7 (89.2–96.3))	74/77 (96.1 (89.2–98.7))	0.8
Pregnancies with liveborn infant				
Possible vertical transmission	1/251 (0.4 (0.1–2.2))	1/177 (0.6 (0.1–3.1))	0/74 (0.0 (0.0–4.9))	0.5
Neonatal death‡	5/251 (2.0 (0.9–4.6))	5/177 (2.8 (1.2–6.4))	0/74 (0.0 (0.0–4.9))	0.14
Admission to NICU	69/251 (27.5 (22.3–33.3))	50/177 (28.2 (22.1–35.3))	19/74 (25.7 (17.1–36.7))	0.7
Breastfeeding	101/251 (40.2 (34.4–46.4))	73/177 (41.2 (34.3–48.6))	28/74 (37.8 (27.7–49.3))	0.2
Skin-to-skin postnatal procedure	69/251 (27.5 (22.3–33.3))	51/177 (28.8 (22.6–35.9))	18/74 (24.3 (16.0–35.2))	0.3
Low birth weight	52/251 (20.7 (16.2–26.2))	43/177 (24.3 (18.6–31.1))	9/74 (12.2 (6.5–21.5))	0.022
Cesarean delivery	136/251 (54.2 (48.0–60.2))	100/177 (56.5 (49.1–63.6))	36/74 (48.6 (37.6–59.8))	0.5
Gestational age at delivery (weeks)	37.2 ± 3.9	36.6 ± 4.3	38.6 ± 2.2	< 0.001
Birth weight (g)	2919 ± 772	2821 ± 846	3149 ± 496	0.004

Data are given as *n* (% (95% CI)), *n*/*N* (% (95% CI)) or mean ± SD. *Defined as at least one of the following: admission to intensive care unit (ICU), use of mechanical ventilation or maternal death. †Including only women with first-trimester infection. ‡Including only liveborn infants with 28 days' follow-up. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; NICU; neonatal intensive care unit; SGA, small-for-gestational age.

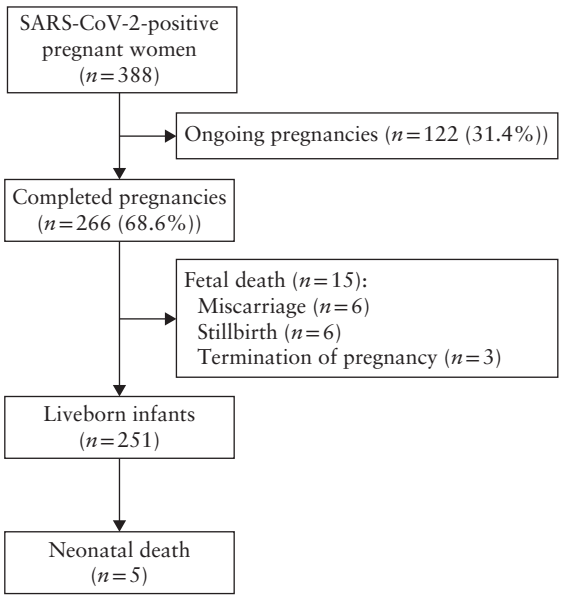

Figure 1 Flowchart summarizing pregnancy outcome of women with SARS-CoV-2 infection.

Predictors of primary outcome

On multivariable analysis restricted to the 266 women with a completed pregnancy (Table 3), the only independent predictors of composite adverse maternal outcome were the presence of any COVID-19 symptoms at presentation *vs* no symptoms (aOR 5.11 (95% CI, 1.11–23.6)), shortness of breath at presentation (aOR 3.68 (95% CI, 1.58–8.58)) and increased levels of LDH (aOR 4.13 (95% CI, 1.54–11.1)).

Post-hoc analysis

Post-hoc subgroup analysis according to region showed no statistically significant differences in the rate of composite adverse maternal outcome (Table S2).

DISCUSSION

Main findings

This multicenter study, including 388 pregnant women from 72 different centers, aimed at evaluating the maternal

Table 3 Regression analysis of potential predictors of composite adverse maternal outcome (CAMO) in 266 pregnancies with SARS-CoV-2 infection that were complete by study end date

Variable	*No CAMO* (n = *227*)	*CAMO* (n = *39*)	*Crude OR* (*95% CI*)	*Adjusted OR* (*95% CI*)*	*Adjusted* P*
Living in high-income country	199 (87.7)	34 (87.2)	0.96 (0.35–2.65)‡	—	—
Living in European country	180 (79.3)	30 (76.9)	0.87 (0.39–1.96)	—	—
Healthcare worker	18 (7.9)	1 (2.6)	0.31 (0.04–2.36)	—	—
Smoker	33 (14.5)	2 (5.1)	0.32 (0.07–1.38)	—	—
Pre-existing chronic disease†	99 (43.6)	12 (30.8)	0.57 (0.28–1.19)	—	—
Obese	23 (10.1)	1 (2.6)	0.23 (0.03–1.78)	—	—
Gestational age at infection (weeks)	34.6 ± 7.5	32.1 ± 5.8	0.96 (0.92–1.00)	—	—
Trimester in which diagnosis made					
First	10 (4.4)	0 (0.0)	—	—	—
Second	22 (9.7)	9 (23.1)	2.80 (1.18–6.64)	—	—
Third	195 (85.9)	30 (76.9)	0.55 (0.24–1.26)	—	—
Maternal age (years)	32.6 ± 6.2	31.5 ± 6.6	0.97 (0.92–1.03)	0.95 (0.89–1.01)	0.10
COVID-19 symptoms at diagnosis					
Fever	94 (41.4)	23 (59.0)	2.03 (1.02–4.06)	—	—
Cough	103 (45.4)	23 (59.0)	1.73 (0.87–3.45)	—	—
Rhinorrhea	15 (6.6)	0 (0.0)	—	—	—
Myalgia	30 (13.2)	5 (12.8)	0.97 (0.35–2.66)	—	—
Anosmia	12 (5.3)	1 (2.6)	0.47 (0.06–3.73)	—	—
Shortness of breath	25 (11.0)	17 (43.6)	6.24 (2.93–13.3)	3.68 (1.58–8.58)	0.003
Diarrhea	6 (2.6)	1 (2.6)	0.97 (0.11–8.28)	—	—
Conjunctivitis	3 (1.3)	0 (0.0)	—	—	—
Any symptom	152 (67.0)	37 (94.9)	9.13 (2.14–38.9)	5.11 (1.11–23.6)	0.037
Laboratory findings					
Lymphocytopenia	86 (37.9)	26 (66.7)	3.28 (1.60–6.72)	2.26 (0.99–5.16)	0.053
Thrombocytopenia	20 (8.8)	9 (23.1)	3.10 (1.29–7.44)	—	—
Increased lactate dehydrogenase levels	16 (7.0)	12 (30.8)	5.86 (2.51–13.7)	4.13 (1.54–11.1)	0.005
Pharmacologic treatment					
No specific pharmacologic treatment	131 (57.7)	14 (35.9)	0.41 (0.20–0.83)	0.58 (0.26–1.29)	0.18
Hydroxychloroquine	49 (21.6)	14 (35.9)	2.03 (0.98–4.21)	—	—
Any antibiotic	48 (21.1)	10 (25.6)	1.29 (0.59–2.82)	—	—
Azithromycin	41 (18.1)	4 (10.3)	0.52 (0.17–1.54)	—	—
Low-molecular-weight heparin	44 (19.4)	17 (43.6)	3.21 (1.57–6.56)	—	—
Antiviral drug					
Any antiviral drug	38 (16.7)	13 (33.3)	2.49 (1.17–5.27)	—	—
Lopinavir/ritonavir	32 (14.1)	11 (28.2)	2.39 (1.08–5.28)	—	—

Data are given as *n* (%) or mean ± SD. CAMO was defined as at least one of the following: maternal death, admission to intensive care unit or requiring maternal mechanical ventilation. *Logistic regression model including 266 observations, with area under the receiver-operating-characteristics curve of 0.81; with the exception of maternal age and any pharmacological treatment, which were included *a priori*, variables that were not significant at the 0.1 level in final model were not included to reduce overfitting. †Including diabetes, hypertension or asthma. ‡Reference group: living in middle-income country. OR, odds ratio.

and perinatal outcomes of pregnancies with confirmed SARS-CoV-2. The study showed that, in pregnancies complicated by SARS-CoV-2 infection, the risk of maternal mortality was 0.8%, but about 11% of women required admission to the ICU. Pregnancies affected by SARS-CoV-2 infection were also complicated by preterm birth in 26.3% and perinatal death in 4.1% of cases. The risk of vertical transmission was negligible, with only one neonate confirmed to be positive for SARS-CoV-2 after delivery. Multivariate analysis showed that the only independent predictors of composite maternal mortality and morbidity were the presence of COVID-19 symptoms at presentation, shortness of breath at presentation and increased levels of LDH.

Strengths and limitations

To the best of our knowledge, this study presents data from one of the largest cohorts of women with SARS-CoV-2 infection during pregnancy published so far[5]. The enrollment of only women with laboratory-confirmed SARS-CoV-2 infection, the large sample, the inclusion of both university hospitals and community hospitals from different countries and the multitude of outcomes explored, represent the major strengths of the study. Moreover, no patients were lost to follow-up and no data were missing for the primary outcome.

The major limitation of the study is the inclusion of only high- and middle-income countries. Therefore, data from this study may not be applicable to low-income countries, in which maternal and perinatal outcomes may be even worse. Data on maternal therapy were limited by the non-randomized approach and we also acknowledge potential heterogeneity in management, since a very large number of centers participated in this study. Our population was derived mostly from women referred for suspected COVID-19, owing to symptoms or exposure, and subsequently tested with RT-PCR of nasopharyngeal swabs. Therefore, the percentage of asymptomatic women in our cohort was low. Maternal and perinatal outcomes may be better in a cohort of women who received universal screening for SARS-CoV-2 infection, in which the rate of asymptomatic women can be as high as 88%[15]. We may not have included all infected women referred to our centers. Indeed, asymptomatic women with COVID-19 undiagnosed early in pregnancy who then tested negative later in pregnancy may not have been included. Lack of a control group of pregnant women without COVID-19 makes it difficult to evaluate the increased risk of adverse maternal and perinatal outcomes in women with COVID-19. Data on treatment side-effects and indication for Cesarean delivery were not collected. Therefore, it was not possible to evaluate whether the high rate of Cesarean delivery was related indirectly to COVID-19, for example because of fear of vertical transmission during vaginal delivery or providers' fear of standing near a COVID-19-positive woman for many hours during labor and delivery. The multicenter study design meant that there may have been differences in the criteria for maternal ICU admission. Another major limitation was the use of a composite score of maternal mortality and morbidity as the primary outcome. This choice was due to the fact that each individual component of the primary outcome had a low prevalence in our study population, thus analyzing each outcome separately would have significantly reduced the power of the analysis and therefore the robustness of the results. This also meant that we could not perform meaningful subgroup analysis in view of the very low prevalence of each component of the primary outcome in the study population. The very large number of centers participating in this study made it difficult to ascertain whether each investigator retrieved information for each outcome independently or by record linkage.

Implications for clinical practice and research

Since December 2019, the outbreak of COVID-19 has become a major epidemic worldwide[3]. Patients infected with SARS-CoV-2 may either be asymptomatic or experience mild to severe symptoms, including pneumonia, respiratory failure and death[16–18]. Physiologic maternal adaptations to pregnancy may predispose pregnant women to a more severe course of viral pneumonia, with a higher risk of maternal mortality and morbidity, as reported for influenza or varicella infection[19]. Therefore, prevention and control of COVID-19 among pregnant women have become major concerns for obstetricians. In the last few months, several recommendations have been published[4,20,21], but evidence is limited[22] and based mostly on case series[23–26] and expert opinion[4,20,21,27–30]. Data published so far[5,31,32] have shown that COVID-19 in pregnant women is associated with a relatively high rate of preterm birth and Cesarean delivery, but have provided no evidence of vertical transmission[4,5,17,33].

In the present cohort, the maternal mortality rate was low. We report the death of three symptomatic pregnant women. Very few cases of maternal death related to COVID-19 have been reported so far[17]. Evidence from non-pregnant populations shows that, among critically ill patients with laboratory-confirmed COVID-19 admitted to the ICU, mortality is about 25%[33,34]. In our cohort, the rate of maternal death was 0.8% with an 11% rate of admission to the ICU. Conversely, the 1918 Spanish flu had a mortality rate of 3% in the general population and 37% among pregnant women[35,36], and in 2003, pregnant women with SARS-CoV-1 infection were reported to have a mortality rate of 25%[4].

Our cohort included one case of suspected vertical transmission in a neonate that tested positive on a RT-PCR test of a nasopharyngeal swab soon after birth. The neonate was asymptomatic and had a negative RT-PCR test at 14 days of age. Unfortunately, amniotic fluid was not tested and specimens from the placenta were not obtained, thus making it unclear whether infection occurred *in utero* (antenatal vertical transmission) or immediately before or after birth (perinatal vertical transmission). Dong *et al.*[37] reported a case of a primiparous woman positive for SARS-CoV-2

on RT-PCR of a nasopharyngeal swab, who delivered by Cesarean section in a negative-pressure isolation room. Results from five RT-PCR tests of nasopharyngeal swabs in the neonate taken from 2 h to 16 days of age were negative, but the infant had elevated antibody levels and abnormal cytokine test results 2 h after birth. The elevated immunoglobulin M (IgM) antibody level may suggest that the neonate was infected *in utero*, given that IgM antibodies are not transferred to the fetus via the placenta[38]. However, no positive RT-PCR test results were obtained in infant specimens, so there was no virologic evidence for congenital infection in this case to support the serologic suggestion of *in-utero* transmission[39]. Notably, IgM may also reach the fetal circulation in cases of placental inflammation[40]. Moreover, sensitivity and specificity of IgM tests vary according to disease, but are usually less reliable than molecular diagnostic tests based on nucleic acid amplification and detection[41]. Indeed, congenital infections are usually not diagnosed based on the detection of IgM because IgM assays can be prone to false-positive and false-negative results, along with cross-reactivity and testing challenges[40,41]. Another case of potential perinatal vertical transmission occurring during vaginal delivery in a pregnant women with rectal and stool maternal swabs that tested positive for SARS-CoV-2 has been reported recently by Carosso *et al.*[33]. The authors concluded that SARS-CoV-2 can enter the neonatal nasopharynx and potentially trigger neonatal infection[33,42].

Different therapies have been proposed for the treatment of COVID-19. Agents used previously to treat SARS and MERS are potential candidates for treating SARS-CoV-2, but meta-analysis of SARS and MERS therapies found no clear benefit of any specific regimen[43–45]. Published clinical experiences have shown that hydroxychloroquine, azithromycin and antiviral drugs, including Kaletra (lopinavir/ritonavir), darunavir/cobicistat or other antiretrovirals, Arbidol (umifenovir), remdesivir or favipiravir are the most promising drugs for the treatment of COVID-19[43,46]. In the present study, 42.8% (166/388) of women received a pharmacologic treatment, such as hydroxychloroquine, azithromycin, antiviral drug or low-molecular-weight heparin. The very small number of events, inclusion of a heterogeneous population of pregnant women and lack of a randomized study design did not allow us to ascertain any evidence on the effectiveness of pharmacologic therapy in our cohort. In the absence of proven therapy, currently, the care of patients with SARS-CoV-2 infection should be based mostly on supportive care, but further evidence is needed before drawing any robust conclusions[47].

Conclusions

In conclusion, SARS-CoV-2 infection in pregnant women is associated with a 0.8% rate of maternal mortality, but an 11.1% rate of admission to the ICU. The risk of vertical transmission seems to be negligible.

The WAPM (The World Association of Perinatal Medicine) Working Group on COVID-19

Gabriele Saccone[1], Cihat Sen[2], Daniele Di Mascio[3], Alberto Galindo[4], Amos Grünebaum[5], Jun Yoshimatsu[6], Milan Stanojevic[7], Asim Kurjak[7], Frank Chervenak[5], María José Rodríguez Suárez[8], Zita Maria Gambacorti-Passerini[9], María de los Angeles Anaya Baz[9,10], Esther Vanessa Aguilar Galán[9,10], Yolanda Cuñarro López[11], Juan Antonio De León Luis[11], Ignacio Cueto Hernández[11], Ignacio Herraiz[4], Cecilia Villalain[4], Roberta Venturella[12], Giuseppe Rizzo[13,14], Ilenia Mappa[13], Giovanni Gerosolima[15], Lars Hellmeyer[16], Josefine Königbauer[16], Giada Ameli[16], Tiziana Frusca[17], Nicola Volpe[17], Giovanni Battista Luca Schera[17], Stefania Fieni[17], Eutalia Esposito[18], Giuliana Simonazzi[19], Gaetana Di Donna[19], Aly Youssef[19], Anna Nunzia Della Gatta[19], Mariano Catello Di Donna[20], Vito Chiantera[20], Natalina Buono[20], Giulio Sozzi[20], Pantaleo Greco[21], Danila Morano[21], Beatrice Bianchi[21], Maria Giulia Lombana Marino[21], Federica Laraud[22], Arianna Ramone[22], Angelo Cagnacci[22], Fabio Barra[22], Claudio Gustavino[22], Simone Ferrero[22], Fabio Ghezzi[23], Antonella Cromi[23], Antonio Simone Laganà[23], Valentina Laurita Longo[24,25,26], Francesca Stollagli[25], Angelo Sirico[24], Antonio Lanzone[24,25], Lorenza Driul[27], Fabiana Cecchini[27], Serena Xodo[27], Brian Rodriguez[28], Felipe Mercado-Olivares[28], Deena Elkafrawi[28], Giovanni Sisti[28], Rosanna Esposito[1], Antonio Coviello[1], Marco Cerbone[1], Maddalena Morlando[29], Antonio Schiattarella[29], Nicola Colacurci[29], Pasquale De Franciscis[29], Ilaria Cataneo[30], Marinella Lenzi[30], Fabrizio Sandri[30], Riccardo Buscemi[31], Giorgia Gattei[31], Francesca della Sala[31], Eleonora Valori[31,32], Maria Cristina Rovellotti[31], Elisa Done[33], Gilles Faron[33], Leonardo Gucciardo[33], Valentina Esposito[34], Flaminia Vena[3], Antonella Giancotti[3], Roberto Brunelli[3], Ludovico Muzii[3], Luigi Nappi[35], Felice Sorrentino[35], Marco Liberati[36], Danilo Buca[36], Martina Leombroni[36], Francesca Di Sebastiano[36], Massimo Franchi[37], Quintino Cesare Ianniciello[37], Simone Garzon[37], Giuliano Petriglia[38], Leonardo Borrello[38], Albaro Josè Nieto-Calvache[39,40], Juan Manuel Burgos-Luna[39,40], Caroline Kadji[41], Andrew Carlin[41], Elisa Bevilacqua[41], Marina Moucho[42], Pedro Viana Pinto[42], Rita Figueiredo[42], José Morales Roselló[43], Gabriela Loscalzo[43], Alicia Martinez-Varea[43], Vincente Diago[43], Jesús S. Jimenez Lopez[44], Yeliz Aykanat[45], Stefano Cosma[46], Andrea Carosso[46], Chiara Benedetto[46], Amanda Bermejo[47], Otto Henrique May Feuerschuette[48], Ozlem Uyaniklar[49], Sakine Rahimli Ocakouglu[49], Zeliha Atak[49], Reyhan Gündüz[50], Esra Tustas Haberal[51], Bernd Froessler[52], Anupam Parange[52], Peter Palm[52], Igor Samardjiski[53], Chiara Taccaliti[54], Erhan Okuyan[55], George Daskalakis[56], Renato Augusto Moreira de Sa[57], Alejandro Pittaro[58], Maria Luisa Gonzalez-Duran[59], Ana Concheiro Guisan[59], Şerife Özlem Genç[60], Blanka Zlatohlávková[61], Anna Luengo Piqueras[62], Dolores Esteban Oliva[62], Aylin Pelin Cil[63], Olus Api[63], Panos

Antsaklis[56], Liana Ples[64], Ioannis Kyvernitakis[65], Holger Maul[65], Marcel Malan[65], Albert Lila[66], Roberta Granese[67], Alfredo Ercoli[67], Giuseppe Zoccali[67], Andrea Villasco[68], Nicoletta Biglia[68], Ciuhodaru Madalina[69], Elena Costa[70], Caroline Daelemans[70], Axelle Pintiaux[70], Elisa Cueto[71], Eran Hadar[72], Sarah Dollinger[72], Noa A. Brzezinski-Sinai[72], Erasmo Huertas[73], Pedro Arango[73], Amadeo Sanchez[73], Javier Alfonso Schvartzman[74], Liviu Cojocaru[75], Sifa Turan[75], Ozhan Turan[75], Maria Carmela Di Dedda[76], Rebeca Garrote Molpeceres[77], Snezana Zdjelar[78], Tanja Premru-Srsen[79], Lilijana Kornhauser-Cerar[79], Mirjam Druškovič[79], Valentina De Robertis[80], Vedran Stefanovic[81], Irmeli Nupponen[81], Kaisa Nelskylä[81], Zulfiya Khodjaeva[82], Ksenia A. Gorina[82], Gennady T. Sukhikh[82], Giuseppe Maria Maruotti[1], Silvia Visentin[83], Erich Cosmi[83], Jacopo Ferrari[83], Alessandra Gatti[84], Daniela Luvero[84], Roberto Angioli[84], Ludovica Puri[25], Marco Palumbo[85], Giusella D'Urso[85], Francesco Colaleo[85], Agnese Maria Chiara Rapisarda[85], Ilma Floriana Carbone[86], Lamberto Manzoli[87], Maria Elena Flacco[87], Giovanni Nazzaro[1], Mariavittoria Locci[1], Maurizio Guida[1], Attilio Di Spiezio Sardo[88], Pierluigi Benedetti Panici[3], Asma Khalil[89,90], Vincenzo Berghella[91], Giuseppe Bifulco[1], Giovanni Scambia[24], Fulvio Zullo[1], Francesco D'Antonio[36]

[1]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy
[2]Perinatal Medicine Foundation and Department of Perinatal Medicine, Memorial Hospital, Istanbul, Turkey
[3]Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Rome, Italy
[4]Fetal Medicine Unit, Maternal and Child Health and Development Network, Department of Obstetrics and Gynecology, University Hospital 12 de Octubre, Complutense University of Madrid, Madrid, Spain
[5]Department of Obstetrics and Gynecology, Lenox Hill Hospital, Zucker School of Medicine at Hofstra/Northwell, New York, NY, USA
[6]Department of Perinatology and Gynecology, National Cerebral and Cardiovascular Center, Osaka, Japan
[7]Department of Obstetrics and Gynecology, Medical School University of Zagreb, Sveti Duh University Hospital, Zagreb, Croatia
[8]Hospital Universitario Central de Asturias, Spain
[9]Department of Obstetrics and Gynecology, Ciudad Real University General Hospital, Ciudad Real, Spain
[10]University of Castilla-La Mancha, Ciudad Real, Spain
[11]Fetal Medicine Unit, Maternal and Child Health and Development Network, Department of Obstetrics and Gynecology, Gregorio Marañón Hospital, Complutense University of Madrid, Madrid, Spain
[12]Department of Obstetrics and Gynaecology, School of Medicine, Magna Graecia University of Catanzaro, Catanzaro, Italy
[13]University of Roma Tor Vergata, Division of Maternal Fetal Medicine, Ospedale Cristo Re Roma, Rome, Italy
[14]Department of Obstetrics and Gynecology, The First I.M. Sechenov Moscow State Medical University, Moscow, Russia
[15]Department of Obstetrics and Gynecology, Ospedale AOSG Moscati, Avellino, Italy
[16]Department of Gynecology and Obstetrics, Vivantes Klinikum im Friedrichshain, Berlin, Germany
[17]Department of Obstetrics and Gynecology, University of Parma, Parma, Italy
[18]Department of Obstetrics and Gynecology, Ospedale di San Leonardo, Castellammare di Stabia, Italy
[19]Department of Obstetrics and Gynecology, University of Bologna, Sant'Orsola Malpighi University Hospital, Bologna, Italy
[20]Department of Gynecologic Oncology, University of Palermo, Palermo, Italy
[21]Department of Medical Sciences, Section of Obstetrics and Gynecology, Azienda Ospedaliera-Universitaria Sant' Anna, University of Ferrara, Ferrara, Italy
[22]Academic Unit of Obstetrics and Gynaecology, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[23]Department of Obstetrics and Gynecology, "Filippo Del Ponte" Hospital, University of Insubria, Varese, Italy
[24]Department of Obstetrics and Gynaecology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[25]Istituto di Clinica Ostetrica e Ginecologica, Università Cattolica del Sacro Cuore, Rome, Italy
[26]Queen Margaret University, Institute for Global Health and Development, Edinburgh, UK
[27]Clinic of Obstetrics and Gynecology, University of Udine, Udine, Italy
[28]Department of Obstetrics and Gynecology, New York Health and Hospitals/Lincoln Bronx, New York, NY, USA
[29]Department of Woman, Child and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy
[30]Unit of Obstetrics and Gynecology, Ospedale Maggiore, Bologna, Italy
[31]Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy
[32]Hospital Castelli, Verbania, Italy
[33]UZ Brussel, Universitair Ziekenhuis, Brussels, Belgium
[34]University of Milan, Milan, Italy
[35]Department of Obstetrics and Gynecology, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy
[36]Centre for High Risk Pregnancy and Fetal Care, Department of Obstetrics and Gynecology, University of Chieti, Chieti, Italy
[37]Department of Obstetrics and Gynecology, AOUI Verona, University of Verona, Verona, Italy
[38]Maternal and Child Health Department, Santa Maria Hospital, Terni, Italy
[39]Fundación Valle del Lili, Tertiary Obstetric Unit, Cali, Colombia
[40]Universidad Icesi, Postgraduate Department, Cali, Colombia
[41]Department of Obstetrics and Gynecology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium
[42]Department of Obstetrics and Gynecology, Centro Hospitalar e Universitário São João, Porto, Portugal
[43]Servicio de Obstetricia y Ginecología, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[44]Hospital Regional Universitario de Málaga, Málaga, Spain
[45]Department of Obstetrics and Gynecology, Istanbul University-Cerrahpasa Medical School, Istanbul, Turkey
[46]Department of Obstetrics and Gynecology, Sant'Anna Hospital, University of Turin, Turin, Italy
[47]Hospital Universitario de Móstoles, Mostoles, Spain
[48]Departamento de Ginecologia e Obstetrícia, Hospital Universitário Polydoro Ernani, Santiago, Brazil
[49]Bursa City Hospital, Bursa, Turkey
[50]Department of Obstetrics and Gynecology, University of Dicle, Diyarbakır, Turkey
[51]Hisar Intercontinental Hospital, Instanbul, Turkey
[52]Department of Anaesthesia, Lyell McEwin Hospital, Adelaide, Australia
[53]University Clinic of Obstetrics and Gynecology, Skopje, North Macedonia
[54]Ospedale Generale Regionale "F. Miulli", Acquaviva delle Fonti, Italy
[55]Batman Maternity and Child Health Hospital, Batman, Turkey
[56]Alexandra Hospital – National and Kapodistrian, University of Athens, Athens, Greece
[57]Assistência Obstétrica do Grupo Perinatal, Rio de Janeiro, Brazil
[58]Hospital Raul F. Larcade, Buenos Aires, Argentina
[59]Alvaro Cunqueiro University Hospital of Vigo, Vigo, Spain
[60]Karaman Public Hospital, Karaman, Turkey

[61]Department of Obstetrics and Gynecology, Division of Neonatology, General Hospital in Prague and First Faculty of Medicine, Charles University, Prague, Czech Republic
[62]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain
[63]American Hospital, Istanbul, Turkey
[64]Department of Obstetrics and Gynecology, St John Hospital, UMF Carol Davila Bucharest, Bucharest, Romania
[65]Asklepios Hospital Barmbek, Hamburg, Germany
[66]Regional Hospital Gjakova, Kosovo, Republic of Kosovo
[67]Department of Obstetrics and Gynecology, University of Messina, Messina, Italy
[68]Academic Division of Obstetrics and Gynecology, Mauriziano Umberto I Hospital, University of Turin, Turin, Italy
[69]Universitatea de Medicină şi Farmacie Grigore T. Popa Iaşi, Iasi, Romania
[70]Department of Obstetrics and Gynecology, Hospital Erasme, Cliniques Universitaires de Bruxells, Brussels, Belgium
[71]Hospital Virgen de la Luz, Cuenca, Spain
[72]Helen Schneider Hospital for Women, Rabin Medical Center, Petach-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[73]Instituto Nacional Materno Perinatal, Lima, Peru
[74]Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno", Buenos Aires, Argentina
[75]Department of Obstetrics, Gynecology and Reproductive Science, University of Maryland Medical Center, Baltimore, MD, USA
[76]Department Gynecology and Obstetrics, Fornaroli Hospital, Magenta, Italy
[77]University Clinic Hospital of Valladolid, Valladolid, Spain
[78]Kbc Dr Dragisa Misovic Dedinje, Belgrade, Serbia
[79]Department of Perinatology, University Medical Center, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia
[80]Fetal Medicine Unit, Di Venere Hospital, Bari, Italy
[81]Department of Obstetrics and Gynecology, Neonatology and Intensive Care, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[82]National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia
[83]Department of Woman's and Child's Health, University of Padova, Padova, Italy
[84]Campus Bio Medico, University of Rome, Rome, Italy
[85]Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy
[86]Ospedale Maggiore Policlinico Milano, Milan, Italy
[87]Department of Medical Sciences, University of Ferrara, Italy
[88]Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy
[89]Fetal Medicine Unit, St George's Hospital, London, UK
[90]Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK
[91]Maternal Fetal Medicine Division, Obstetrics and Gynecology Department, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 List of centers included in study

Table S1 Characteristics of 43 pregnant women with SARS-CoV-2 infection who were admitted to intensive care unit

Table S2 Maternal and perinatal outcomes of 388 pregnancies with SARS-CoV-2 infection, according to region

