

## **Clinical Findings and Disease Severity in Hospitalized Pregnant Women With Coronavirus Disease 2019 (COVID-19)**

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## **OBJECTIVE:**

To investigate the clinical evolution of coronavirus disease 2019 (COVID-19) in hospitalized pregnant women and potential factors associated with severe maternal outcomes.

## **METHODS:**

We designed a prospective multicenter cohort study of pregnant women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were admitted to 12 Italian maternity hospitals between February 23 and March 28, 2020. Clinical records, laboratory and radiologic examinations, and pregnancy outcomes were collected. A subgroup of patients with severe disease was identified based on intensive care unit (ICU) admission, delivery for respiratory compromise, or both.

## **RESULTS:**

Seventy-seven patients were included, 14 of whom had severe disease (18%). Two thirds of the patients in the cohort were admitted during the third trimester, and 84% were symptomatic on admission. Eleven patients underwent urgent delivery for respiratory compromise (16%), and six were admitted to the ICU (8%). One woman received extracorporeal membrane oxygenation; no deaths occurred. Preterm delivery occurred in 12% of patients, and nine newborns were admitted to the neonatal intensive care unit. Patients in the severe subgroup had significantly higher pregestational body mass indexes (BMIs) and heart and respiratory rates and a greater frequency of fever or dyspnea on admission compared with women with a nonsevere disease evolution.

## **CONCLUSION:**

In our cohort, one in five women hospitalized with COVID-19 infection delivered urgently for respiratory compromise or were admitted to the ICU. None, however, died. Increased pregestational BMI and abnormal heart and respiratory rates on admission were associated with severe disease.

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which represents a worldwide public health emergency. After the first case of COVID-19 pneumonia was identified in Wuhan, China, in December 2019, the infection spread rapidly. Italy has been particularly affected by COVID-19.<sup>1-3</sup> Patients with infection may be asymptomatic or they may experience mild to severe illness, including pneumonia, respiratory failure, and death.<sup>4-7</sup>

Despite maternal physiologic adaptations to pregnancy, which are known to increase the risk of severe illness in response to viral infections, the few available data do not support a greater susceptibility to severe COVID-19 infections in pregnant women than in the general population.<sup>8,9</sup> There are currently no data suggesting an increased risk of miscarriage, congenital anomalies, or early pregnancy loss in pregnant patients with COVID-19 infection; an increased risk of preterm birth has been described.<sup>10</sup> Personalized management has been advocated in pregnant and postpartum patients with infection who have severe disease, and elective birth is indicated to assist efforts in maternal resuscitation on a case-by-case basis.<sup>10,11</sup> Because there is a paucity of pregnancy data, we aimed in this cohort study to present clinical features and the evolution of confirmed maternal SARS-CoV-2 infection at different gestational ages and, secondly, to investigate potential factors associated with severe maternal disease and iatrogenic delivery.

## **METHODS**

This is a prospective multicenter study, including women with laboratory-confirmed SARS-CoV-2 infection who were admitted during pregnancy or the immediate postpartum period in 12 maternity hospitals in Northern Italy between February 23 and March 28, 2020, including L. Sacco (Milan), Mangiagalli (Milan), S. Gerardo MBBM Foundation (Monza), Papa Giovanni XXIII (Bergamo), and San Matteo (Pavia) as hub maternity hospitals, and Hospitals of Padua, Florence, Lecco, Trento, Modena, Seriate and Piacenza. The protocol was approved by the local Medical Ethical and Institutional Review Board (approval number 15408/2020).

Included patients were admitted at any gestational age or within the third postpartum day with a diagnosis of SARS-CoV-2 infection, identified by a positive result on a reverse transcriptase polymerase chain reaction assay of a maternal nasopharyngeal swab specimen. According to the Italian guidelines, during the study period, only those patients with symptoms or known contacts with individuals with suspected or confirmed COVID-19 infection were tested. The swab samples were processed by using reverse transcriptase polymerase chain reaction testing SARS-CoV-2 with the automated ELITE InGenius system and the GeneFinder COVID-19 Plus RealAmp Kit assay, according to manufacturer's instructions. This assay targets three genes: RNA-dependent RNA

polymerase, nucleocapsid protein, and envelope membrane protein, with high specificity. Test results were obtained within 24 hours. All included women underwent clinical evaluation of vital signs and symptoms, laboratory analysis, and radiologic chest assessment at admission at the discretion of the treating physician. Therapeutic management was consequently tailored according to the clinical findings and guidelines.<sup>12</sup> Demographic and anthropometric characteristics, lifestyle habits, medical or obstetric comorbidities, and epidemiologic contacts with individuals with suspected or confirmed COVID-19 infection were recorded at enrollment through a customized data-collection form. All women underwent fetal growth and well-being assessment and obstetric management, as required by local standard protocols.

Maternal venous blood sample analysis was performed every 48 hours, including hemoglobin, white blood cell count, hepatic and renal function tests (alanine aminotransferase, aspartate aminotransferase, creatinine), and inflammation markers (C-reactive protein). Data on COVID-19 treatments, clinical evolution during pregnancy, need for oxygen support, and intensive care unit (ICU) admission were collected. Data on mode of delivery or pregnancy termination, neonatal outcomes, and postpartum maternal clinical evolution were subsequently recorded. A subgroup of patients with severe disease was identified based on: 1) urgent delivery based on maternal respiratory function, 2) ICU or subintensive care admission during pregnancy or the postpartum period, or 3) both 1 and 2. All collected data were transferred to an electronic database, and data accuracy was independently verified by two study investigators (V.M.S. and F. Parisi). Any discrepancy or unclear information was verified with the specific participating center.

Medians and ranges were reported for quantitative study variables, and absolute and relative frequencies were reported for categorical variables. Baseline characteristics and pregnancy and birth outcomes were compared between patients in the severe and nonsevere groups using  $\chi^2$  or exact tests for ordinal variables and Mann-Whitney U test for continuous variables. No imputation was made for missing data. The analyses were performed using SPSS Statistics 26.0.

## RESULTS

Seventy-seven patients with confirmed SARS-CoV-2 infection were included (Table 1). Fourteen patients (18%) were classified as having severe disease, defined by the need of urgent delivery for the deterioration of respiratory status or by ICU or subintensive care admission (or both). Ten patients (13%) were symptomatic and diagnosed with SARS-CoV-2 infection in the postpartum period within 3 days after delivery; four patients were admitted during the first trimester (5%), 13 during the second trimester (17%), and 50 during the third trimester (65%).

Twelve of the 77 patients (16%) were asymptomatic and admitted for obstetric indications, including labor, pregnancy complications, planned cesarean delivery, and labor induction. These patients received a nasopharyngeal swab specimen test because of a reported contact with an individual with known COVID-19 infection. Chest imaging was performed among 43 symptomatic patients on admission, and 34 (79%) were diagnosed with interstitial pneumonia. During the antepartum period of hospitalization, 43% of the symptomatic patients received empiric antibiotic therapy (mostly penicillins or cephalosporins or macrolides or both), 38% received antiviral therapy (lopinavir–ritonavir, remdesivir, or darunavir), and 30% received hydroxychloroquine, with all of the patients with severe disease receiving combined therapies. Anticoagulant prophylaxis was administered to 22 patients (39%), including all of the patients with severe disease, based on the independent decision of the treating physician. Of 67 patients with an antepartum diagnosis of COVID-19 infection, 11 underwent delivery for respiratory indications (16%).

Fourteen patients were classified as having severe disease because of antepartum (n=1) or postpartum (n=5) ICU admission, receipt of continuous positive airway pressure ventilation in a subintensive care department (n=2), or urgent delivery based on maternal respiratory illness without ICU admission (n=6). On admission, gestational ages in the patients with severe disease were 9, 24, 25 (n=2), 27, 28, 33, 37 (n=5), and 39 (n=2) weeks. Pregestational obesity (n=7), chronic hypertension (n=1), and advanced maternal age (older than 40 years, n=1) were noted in the severe subgroup, but 5 of 14 patients had no known risk factors for severe complications on admission. When compared with patients in the nonsevere group, those in the severe subgroup showed significantly increased pregestational body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), respiratory and heart rates on admission, and higher prevalence of fever and dyspnea (Table 1). Radiologic confirmation of interstitial pneumonia was obtained on admission or antepartum for all of the patients in the severe subgroup, except for one patient who underwent emergency cesarean delivery without a radiologic chest assessment. No differences in laboratory and blood gas analysis data were detected between patients in the severe and nonsevere groups on admission (Table 2).

Cesarean delivery was performed in 9 of the 11 patients with severe disease who underwent urgent delivery for respiratory compromise (Fig. 1). Significant postpartum improvement in maternal clinical conditions was detected among six patients with severe disease. The patient with the most severe disease (number 14, Fig. 1), admitted at 37 weeks of gestation for fever and dyspnea, showed a rapid deterioration of respiratory function during the first hospitalization day (oxygen saturation 90% under oxygen support 10 L/min), prompting an emergency cesarean delivery. Owing to the rapid postpartum deterioration of maternal respiratory function, vital signs, and blood gas analysis

(PaO<sub>2</sub> 50 mm Hg), the patient was admitted to the ICU and underwent venovenous extracorporeal membrane oxygenation for 14 days, with subsequent improvement in clinical conditions. No maternal deaths occurred in this series.

Twenty patients were still pregnant at discharge. The remaining 57 patients underwent vaginal delivery or cesarean delivery during the hospitalization period (see Table 3 for details). Nine newborns were admitted to the neonatal intensive care unit. Four (three vaginal deliveries and one cesarean delivery) of 57 were diagnosed with SARS-CoV-2 infection in the early postpartum period, none in the severe subgroup. For all these newborns, rooming-in and breastfeeding were performed. None of the newborns subsequently developed respiratory symptoms.

## DISCUSSION

The present study shows the clinical maternal evolution of SARS-CoV-2 infection among 77 hospitalized pregnant patients in Northern Italy. Most were admitted during the third trimester (65%). Only four patients were hospitalized during the first trimester of pregnancy, one of whom received continuous positive airway pressure ventilation in a subintensive care unit.

Infection with COVID-19 caused moderate to severe respiratory illness in 18% of the patients in the study cohort. Oxygen support was used in 29% and 15% of the patients during the antepartum and postpartum period, respectively; 8% had ICU admission, and 16% underwent urgent delivery. Three patients were intubated after emergency cesarean delivery performed for maternal deterioration, and one patient underwent extracorporeal membrane oxygenation. Our results are in line with epidemiologic data among the nonpregnant population, where approximately 80% of SARS-CoV-2 infections are mild or asymptomatic, 15% require supplemental oxygen, and 5% require mechanical ventilation.<sup>2</sup> Nevertheless, no maternal deaths were observed in our cohort. It is conceivable that physiologic immune adaptations to pregnancy, including transition to a T-helper 2 environment and increased expression of antiinflammatory cytokines, may influence the immunologic responses to SARS-CoV-2 infection, resulting in a less severe COVID-19 course compared with nonpregnant individuals.<sup>13</sup>

In our cohort, the main factors associated with maternal severe outcomes were increased pregestational BMI, higher heart and respiratory rates, and presence of fever and dyspnea on admission. In particular, pregestational BMI was significantly higher in the patients in the severe subgroup, with 7 of 14 women being obese (50%). Overweight and obesity have a prevalence of 9% in the pregnant population of Lombardy (epidemiologic data from 2019 registries) and are known risk factors for both morbidity in pregnancy and COVID-19 severity.<sup>14,15</sup> Additionally, 31% of our population showed chronic comorbidities and 27% an obstetric complication, suggesting that

comorbidities may also play a role in SARS-CoV-2 infection in pregnancy. On the other hand, in contrast to the nonpregnant population, maternal age was statistically comparable between patients with severe and nonsevere disease; the smaller age range of the reproductive period may explain this result.<sup>7</sup>

Preterm delivery was the main obstetric adverse outcome, with seven patients undergoing spontaneous preterm or respiratory-indicated delivery (12% vs 7% in the same areas in 2019). We also noted a high cesarean delivery rate in the study population (39% vs 27% in the same area in 2019), mainly as a result of maternal respiratory-indicated urgent delivery. Significant postpartum improvement in maternal clinical condition was noted in approximately 55% of patients, but 45% of those with severe disease undergoing maternal-indicated cesarean delivery were subsequently admitted to the ICU. In line with recent Italian reports of a 12 times higher maternal mortality rate after cesarean compared with vaginal delivery, we cannot exclude that surgical delivery could aggravate maternal antepartum inflammatory and endothelial dysfunction in this subgroup, thus leading to postpartum ICU admission.<sup>16</sup> Interestingly, besides prematurity, fetal oxygenation and well-being at delivery were not apparently affected by the maternal acute conditions.

In the nonsevere subgroup, three newborns with vaginal delivery tested positive on SARS-CoV-2 swab specimen testing on the first day of life and one newborn with cesarean delivery tested positive on the seventh day. Because no data on blood immunoglobulins are available, it seems likely that the newborns may have been infected after delivery.

There is no currently validated treatment to control SARS-CoV-2 infection, especially in pregnancy. This explains the nonuniform therapeutic management noted in our series, with antiviral therapy being administered to one third of patients in the nonsevere group and two thirds of patients in the severe group and anticoagulant prophylaxis based on the severity of clinical evolution and prolonged bedrest.

Despite the large number of pregnant women with SARS-CoV-2 infection included, this study has several limitations. First, this is a multicenter study, so criteria for hospital admission and therapeutic protocols may have been different. This also explains missing data, owing to the emergency situation and communication difficulties. Third, some cases early in the outbreak could have been missed, and follow-up is still limited. Finally, this series includes patients admitted before the recent approval of a universal SARS-CoV-2 infection screening policy aimed at the hospitalized pregnant population. This explains the high rate of maternal severe outcomes, because the diagnosis was mostly related to symptomatic patients.

In summary, we observed severe outcomes in a significant proportion of hospitalized pregnant and postpartum women with COVID-19 infection in Northern Italy, with no maternal deaths. Increased

BMI was a significant risk factor for severe disease. Fever and dyspnea on admission were symptoms significantly associated with subsequent severe maternal respiratory deterioration. Prematurity was the most prevalent adverse perinatal outcome.

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**Table 1.** Baseline Characteristics of the Study Population on Admission and Therapeutic Management

Enrollment Characteristics	Total Study Population (N577)	Severe Subgroup (n514)	P*
<b>Maternal characteristics</b>			
Gestational age (d)	261 (37–287)	235 (63–278)	.08
Maternal age (y)	32 (15–48)	30 (18–40)	.35
Prepregnancy BMI (kg/m <sup>2</sup> )	22.8 (17.5–54.1)	30 (19.4–54.1)	<b>.02</b>
Gestational weight gain (kg)	10 (0–24)	12 (6–16)	.59
Known sick contact	27 (39)	5 (46)	.63
Smoking	1 (1)	0 (0)	.64
Ethnicity, white	53 (69)	8 (57)	.29
Chronic comorbidity†	24 (32)	6 (46)	.21
Parity, nulliparous	30 (40)	6 (46)	.24
Flu vaccination in pregnancy	14 (22)	2 (17)	.62
<b>Baseline symptoms</b>			
Fever	41 (54)	13 (93)	<b>&lt;.01</b>
Cough	50 (66)	12 (86)	.08
Dyspnea	19 (25)	8 (57)	<b>&lt;.01</b>
<b>Vital signs</b>			
Respiratory rate (breaths per minute)	18 (7–30)	25 (18–30)	<b>&lt;.01</b>
Greater than 20	29 (43)	10 (77)	
Heart rate (beats per minute)	95 (57–144)	110 (57–130)	<b>.02</b>
Greater than 100	25 (37)	7 (58)	
Percutaneous oxygen saturation	98 (85–100)	96 (90–100)	.07
Greater than 95%	13 (18)	4 (31)	
<b>Antepartum therapy</b>			
Antibiotic	27 (43)	10 (77)	<b>&lt;.01</b>
Antiviral	25 (38)	8 (62)	<b>.01</b>
Hydroxychloroquine	19 (30)	6 (46)	<b>&lt;.01</b>
Oxygen support without ICU admission	20 (29)	11 (79)	<b>&lt;.01</b>

BMI, body mass index; ICU, intensive care unit.

Data are median (range) or n (%) unless otherwise specified. Percentages are expressed as valid frequencies after excluding missing values. Bold indicates significant results.

\* The comparison was performed between patients in the severe (n514) and nonsevere (n563) groups by using  $\chi^2$  or exact tests for ordinal variables and Mann-Whitney U test for continuous variables.

† Chronic comorbidity includes obesity and cardiovascular, autoimmune, endocrine, and metabolic diseases.

**Table 2.** Laboratory, Radiologic, and Blood Gas Analysis Data on Admission

	Total Study Population (n577)	Severe Subgroup (n514)	P*
Laboratory data (n556)			
WBC count ( $\times 10^9/L$ )	7.79 (3.25–17.50)	8.23 (5.10–15.00)	.86
Lymphocytopenia	19 (29)	5 (46)	.18
Hb greater than 11 g/dL	22 (39)	4 (50)	.20
AST greater than 40 units/L	16 (41)	5 (63)	.06
ALT greater than 40 units/L	12 (19)	3 (23)	.27
Lactate dehydrogenase greater than 250 units/L			
	16 (39)	3 (50)	.31
Serum creatinine, median (range)	0.59 (0.40–1.83)	0.67 (0.46–0.80)	.56
C-reactive protein greater than 10 mg/L	39 (61)	9 (64)	.51
Blood gas analysis (n521), abnormal†	12 (57)	6 (86)	.06
Radiologic findings (n543), pneumonia‡	30 (70)	9 (75)	.64

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin; WBC, white blood cell.

Data are median (range) or n (%) unless otherwise specified. Percentages are expressed as valid frequencies after excluding missing values.

\* The comparison was performed between patients in the severe (n514) and nonsevere (n563) groups by using  $X^2$  or exact tests for ordinal variables and Mann-Whitney U test for continuous variables.

† Blood gas analysis was performed among 21 patients admitted with abnormal vital signs.

‡ Radiologic chest assessment was performed among 43 patients on admission.

**Table 3.** Maternal and Pregnancy Outcomes in a Subset of the Study Population Undergoing Vaginal or Cesarean Delivery During Hospitalization\*

Outcome	Total Study Population (n557)	Severe Subgroup (n511)	P†
Delivery mode			
Vaginal	34 (61)	2 (18)	<b>&lt;.01</b>
Cesarean	22 (39)	9 (82)	
Gestational age at delivery (d)	272.5 (175–289)	262 (175–280)	<b>.01</b>
Preterm delivery	12 (21)	4 (36)	.08
Maternal respiratory indication for delivery	11 (16)	11 (100)	<b>&lt;.01</b>
Blood loss (mL)	400 (50–3,000)	500 (100–1,000)	.78
Neonatal sex, male	28 (49)	4 (36)	.36
Birth weight (g)	3,160 (840–4,350)	3,275 (840–3,770)	.42
Umbilical artery pH	7.30 (6.94–7.53)	7.30 (7.21–7.40)	.92
5-min Apgar score	10 (4–10)	10 (5–10)	.32
Newborn COVID-19 test result, positive	4 (7)	0 (0)	.41
NICU admission	9 (16)	4 (40)	.07
Postpartum ICU admission	5 (9)	5 (45)	<b>&lt;.01</b>
Postpartum therapy			
Antibiotic	19 (35)	6 (75)	.18
Antiviral	16 (29)	5 (63)	.36
Hydroxychloroquine	19 (35)	7 (88)	<b>.03</b>
Oxygen support without ICU admission	8 (15)	1 (17)	<b>.04</b>

GA, gestational age; NICU, neonatal intensive care unit.

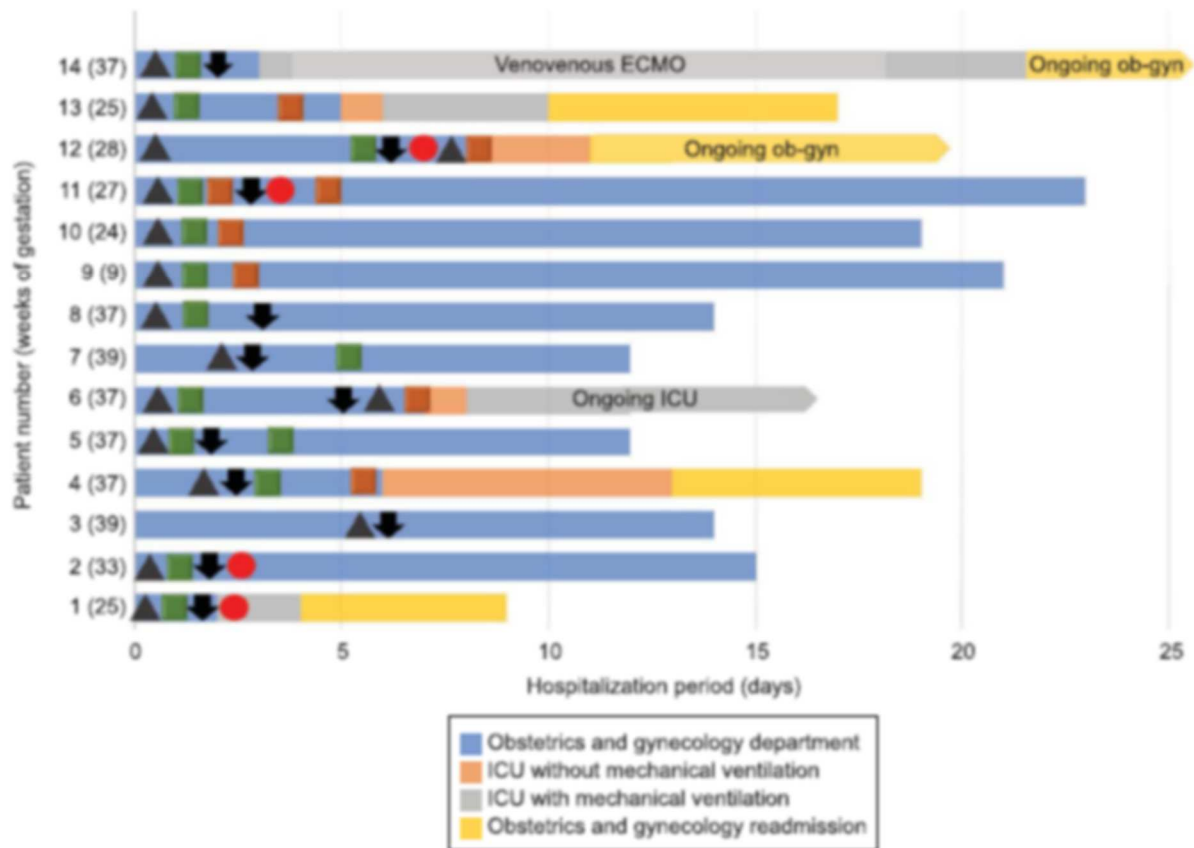
Data are median (range) or n (%) unless otherwise specified. Percentages are expressed as valid frequencies after excluding missing values.

Bold indicates significant results.

\* Pregnancy outcomes are shown for patients the severe and nonsevere groups who underwent vaginal or cesarean delivery during the hospitalization period.

† The comparison was performed between patients in the severe (n511) and nonsevere (n546) groups by using  $X^2$  or exact tests for ordinal variables and Mann-Whitney U test for continuous variables.

Fig. 1.



Clinical evolution of patients with coronavirus disease 2019 (COVID-19) infection with severe disease during the hospitalization period. Fourteen patients were classified as having severe disease based on intensive care unit (ICU) or subintensive care admission with or without need for urgent delivery owing to maternal respiratory deterioration. Need for oxygen support (*green square*), noninvasive mechanical ventilation (continuous positive airway pressure ventilation, *orange square*), urgent delivery (*black arrow*), and neonatal intensive care unit admission (*red circle*) are shown. All patients showed vital sign and laboratory or blood gas analysis alterations during the antepartum hospitalization period (*grey triangle*) and were diagnosed with interstitial pneumonia. Currently ongoing hospitalizations are shown. ECMO, extracorporeal membrane oxygenation.