Outcomes of Critically Ill Pregnant Women with COVID-19 in the United States

To the Editor:

Data from viral respiratory illnesses such as influenza, severe acute respiratory syndrome coronavirus 1, and Middle East respiratory syndrome suggest that viral respiratory infection during pregnancy may worsen both maternal and fetal outcomes (1, 2). Existing data in critically ill pregnant women with coronavirus disease (COVID-19) are mainly limited to case series or systematic reviews lacking nonpregnant control subjects (3–5). To better understand this potentially at-risk population, we describe the clinical course of 32 critically ill pregnant women admitted to ICUs across the United States. Furthermore, we compare the characteristics, treatment, and outcomes of these pregnant women with those of women who were not pregnant at the time of ICU admission.

We used data from STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19), a multicenter cohort study of critically ill adults with laboratory-confirmed COVID-19 admitted to 67 participating ICUs across the United States (6). For the current analysis, we included all COVID-19–positive pregnant women admitted to ICUs between March 4 and May 2, 2020. We matched each pregnant woman with two nonpregnant women according to age (±2 yr) and the Quick Sequential Organ Failure Assessment (qSOFA) score at admission to the ICU (7). For purposes of matching, we dichotomized the qSOFA score into lower risk (score of 0–1) and higher risk (score of 2–3). All patients were followed up until hospital discharge, death, or a minimum of 28 days after ICU admission. We compared outcomes between pregnant and nonpregnant women using chi-square or Fisher exact tests for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Among 4,145 patients in the parent cohort, we identified 32 pregnant women and matched these to 64 nonpregnant women. The median age in both groups was 32 years (interquartile range, 27–35). In both groups, 62.5% of patients had a qSOFA score of 2 or 3 at admission. The frequency and severity of acute respiratory failure, assessed by receipt of invasive mechanical ventilation and the Pa_{O_2}/FI_{O_2} ratio at ICU admission, were similar between groups (Table 1).

Pregnant women were more likely to receive remdesivir (50.0% vs. 10.9%) and less likely to receive tocilizumab than nonpregnant women (9.4% vs. 23.4%). The rate of invasive mechanical ventilation, prone positioning, and neuromuscular blockade during the 14 days after ICU admission was similar between groups. The incidences of venous thromboembolism and other acute organ injuries, together with ICU and hospital length of stay, were similar between groups (Table 1). There were no maternal or fetal deaths, whereas 6 of the 64 nonpregnant women (9.4%) died during hospitalization.

A total of 19 women (59.3%) delivered during the hospitalization, with 11 of the 19 deliveries (57.9%) occurring on the day of ICU admission. Among the 19 deliveries, 18 (94.7%) were preterm, defined as occurring at less than 37 weeks' gestation. Only three of these preterm births were spontaneous, with the remainder performed for medical or obstetric indications. The most common indications for delivery were maternal respiratory failure (52.6%), spontaneous labor or rupture of membranes (25.0%), and nonreassuring fetal status (21.1%) (Table 2). A total of 17 of the 19 women (89.5%) who delivered underwent cesarean section, with maternal critical illness reported as the most common indication (41.2%). Among the 17 women with pregnancies at more than 30 weeks' gestation at ICU admission, 15 (88.2%) delivered, as compared with 4 out of 15 (26.7%) who delivered at less than 30-weeks' gestation.

Unlike prior viral pandemics (1–4), maternal and fetal outcomes among critically ill pregnant women with COVID-19 in our cohort were excellent, with no reported deaths. Consistent with prior COVID-19 studies in pregnant women, our study found high rates of cesarean delivery and preterm birth (3–5). The majority of preterm delivery occurred in the setting of maternal respiratory failure, with a high rate of cesarean delivery for this indication. Complex medical decision-making is required in the management of critically ill pregnant women. The decision regarding delivery needs to balance multiple risks and benefits, including the risks of prematurity to the fetus, the potential to improve or worsen maternal respiratory status with delivery, and the known maternal hemodynamic and inflammatory burden accompanying major surgery such as cesarean section (8). Pregnant women in our cohort at less than 30-weeks' gestation at the time of ICU admission were less likely to undergo delivery, which may reflect attempts to maximize fetal survival.

Pregnant women in our cohort had lower mortality than age- and qSOFA-matched nonpregnant women. This finding may reflect the lower burden of comorbidities among pregnant women in our small cohort. Notably, a recently published case series from Iran reported a high rate of mortality (77.8%) among nine critically ill pregnant women with COVID-19 (9). Potential reasons for the vastly different outcomes observed in the pregnant women in our cohort include differences in healthcare delivery systems, patient risk factors, and an apparently low threshold for ICU admission for pregnant patients with COVID-19 in our cohort. We followed patients until hospital discharge, but our cohort lacks long-term follow-up data, including neonatal outcomes. Both pregnancy and COVID-19 raise the risk of thromboembolic disease, highlighting the need for long-term follow-up data in pregnant and postpartum women with COVID-19.

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Author Contributions: S.R.E., S.G., and D.E.L. conceived the study, had full access to the data in the study, and take responsibility for the integrity of the data and accuracy of the analyses. S.R.E., S.G., S.K.B., and D.E.L. wrote the manuscript. S.R.E. performed the statistical analyses. S.R.E. designed the tables. S.R.E., S.G., S.K.B., and D.E.L. acquired the data. All authors provided feedback on the protocol and critically revised and approved the final version to be published.

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Table 1. Characteristics, Therapies, and Outcomes according to Pregnancy Status

Characteristic	Pregnant (*N* = 32)	Nonpregnant (*N* = 64)	*P* Value
Age, yr, median (IQR)	32 (27–35)	32 (27–35)	0.99
qSOFA score at ICU admission			0.99
0–1	12 (37.5)	24 (37.5)	
2–3	20 (62.5)	40 (62.5)	
Race, *n* (%)			0.49
White	10 (31.2)	23 (35.9)	
Black	7 (21.9)	20 (31.2)	
Asian	3 (9.4)	4 (6.2)	
More than one or not reported	12 (37.5)	17 (26.5)	
Hispanic ethnicity, *n* (%)	9 (28.1)	20 (31.3)	0.75
Body mass index, kg/m^2, median (IQR)*	33.7 (27.0–38.2)	36.7 (29.9–42.2)	0.10
Coexisting conditions, *n* (%)			
Diabetes mellitus	4 (12.5)	22 (34.4)	0.02
Hypertension	3 (9.4)	16 (25.0)	0.07
Asthma	9 (28.1)	16 (25.0)	0.74
Chronic kidney disease	1 (3.1)	2 (3.1)	0.99
Time from symptom onset to ICU admission, d, median (IQR)	7 (5–10)	NA	NA
Vital signs on day of ICU admission, median (IQR)			
Temperature, °C*	37.5 (37.0–38.0)	38.4 (37.3–39.3)	<0.01
Systolic blood pressure, mm Hg	99 (91–110)	99 (89–106)	0.64
Heart rate, beats/min	116 (108–128)	119 (102–132)	0.81
Respiratory rate, breaths/min	28 (23–37)	34 (27–40)	0.02
Laboratory findings on day of ICU admission, median (IQR)*			
White blood cell count, $\times 10^9$ cells/L	9.4 (7.8–12.7)	7.6 (5.3–11.1)	0.04
Creatinine, mg/dl	0.5 (0.5–0.7)	0.7 (0.6–0.9)	<0.01
D-dimer, ng/ml	890 (640–1,374)	845 (441–1,688)	0.68
C-reactive protein, mg/L	99 (77–118)	119 (53–237)	0.27
Invasive mechanical ventilation on ICU admission, *n* (%)	18 (56.2)	37 (57.8)	0.88
$Pa_{O_2}/F_{I_{O_2}}$, mm Hg, median (IQR)*†	183 (108–261)	144 (100–230)	0.42
Gestational age at ICU admission, wk, median (IQR)	30.4 (25.8–33.5)	NA	NA
Treatments and organ injury within the first 14 d of ICU admission			
Interventions for hypoxemia, *n* (%)			
Prone position	11 (34.4)	25 (39.1)	0.65
Neuromuscular blockade	9 (28.1)	28 (43.8)	0.14
Inhaled epoprostenol or nitric oxide	3 (9.4)	10 (15.6)	0.40
Medical therapy, *n* (%)			
Remdesivir	16 (50.0)	7 (10.9)	<0.01
Tocilizumab	3 (9.4)	15 (23.4)	0.10
Convalescent plasma	4 (12.5)	6 (9.4)	0.73
Any experimental therapy‡	17 (53.1)	25 (39.1)	0.19
Therapeutic anticoagulation	13 (41.1)	28 (43.8)	0.77
Acute respiratory distress syndrome, *n* (%)	16 (50.0)	16 (50)	0.03
Invasive mechanical ventilation, *n* (%)	23 (71.9)	48 (75.0)	0.74
Mechanical ventilation duration, d, median (IQR)†	11 (6–14)	13 (8–14)	0.53
Vasopressors, *n* (%)	23 (71.8)	23 (71.9)	0.23
Acute kidney injury, *n* (%)§	4 (12.5)	15 (25.0)	0.16
Renal replacement therapy, *n* (%)	0 (0)	6 (10.0)	0.09
Arrhythmia, *n* (%)	1 (3.1)	1 (1.6)	0.99
Extracorporeal membrane oxygenation, *n* (%)	3 (9.4)	3 (4.7)	0.40
Thrombosis, *n* (%)	2 (6.2)	7 (10.9)	0.71
Outcomes			
In-hospital death, *n* (%)‖	0 (0)	6 (9.4)	0.17
ICU length of stay, d, median (IQR)‖	10 (3–18)	13 (5–24)	0.28
Hospital length of stay, d, median (IQR)‖	14 (8–24)	11 (5–23)	0.13
Delivered during hospitalization, *n* (%)¶	19 (59.4)	NA	NA
Cesarean delivery, *n* (%)¶	17 (53.1)	NA	NA
Gestational age at delivery, wk, median (IQR)	32.9 (30.1–34.4)	NA	NA

Definition of abbreviations: IQR = interquartile range; NA = not applicable; qSOFA = Quick Sequential Organ Failure Assessment.

*Data were missing for creatinine for 3 nonpregnant patients, C-reactive protein for 10 pregnant and 21 nonpregnant patients, D-dimer for 8 pregnant and 29 nonpregnant patients, and $Pa_{O_2}/F_{I_{O_2}}$ for 10 pregnant and 11 nonpregnant mechanically ventilated patients.

†$Pa_{O_2}/F_{I_{O_2}}$ was only assessed in patients receiving invasive mechanical ventilation. Days of mechanical ventilation were limited to the first 14 days of hospitalization.

‡Experimental therapies were remdesivir, tocilizumab, and convalescent plasma.

§Acute kidney injury was defined as doubling of baseline creatinine or need for renal replacement therapy. Patients with end-stage renal disease ($n = 4$) were excluded.

‖In-hospital mortality data were available for all patients for a minimum of 28 days after ICU admission. Because of ongoing hospitalization, data on ICU length of stay were incomplete for 14 patients, and data on hospital length of stay were incomplete for 24 patients.

¶Indications for delivery were maternal respiratory failure ($n = 10$), fetal status ($n = 5$), spontaneous labor or rupture of membranes ($n = 3$), and preeclampsia ($n = 1$).

Table 2. Case Details of Critically Ill Pregnant Patients with COVID-19

Case*	Gestational Age at ICU Admission (*wk*)	Delivery during Admission	Days between Admission and Delivery	Gestational Age at Delivery (*wk*)	Mode of Delivery	Indication for Delivery	Indication for Cesarean Delivery	$Pa_{O_2}/F_{I_{O_2}}$ on Intubation	Duration of Mechanical Ventilation† (*d*)	ICU Length of Stay† (*d*)	Hospital Length of Stay† (*d*)
1	⩾37	Yes	<1	40.6	Vaginal	Spontaneous labor	NA	513	1	1	5
2	34.0–36.9	Yes	<1	36.4	Cesarean	Respiratory failure	Breech	NA	0	5	8
3	34.0–36.9	Yes	>2	37.0	Cesarean	Fetal status	Fetal heart rate	NA	0	1	8
4	34.0–36.9	Yes	<1	35.6	Cesarean	SROM	Breech	268	6	7	13
5	34.0–36.9	Yes	<1	34.3	Cesarean	Fetal status	Fetal heart rate	117	14	25	35
6	34.0–36.9	Yes	1–2	34.4	Cesarean	Respiratory failure	Critical illness	116	12	12	24
7	28.0–33.9	Yes	>2	34.4	Cesarean	Preeclampsia	Critical illness	NA	0	1	4
8	28.0–33.9	Yes	<1	33.6	Cesarean	Respiratory failure	Uterine surgery	NA	0	1	6
9	28.0–33.9	No	NA	NA	NA	NA	NA	NA	0	1	3
10	28.0–33.9	Yes	<1	33.4	Cesarean	Respiratory failure	Critical illness	101	5	6	14
11	28.0–33.9	Yes	>2	32.9	Cesarean	Respiratory failure	Breech	158	14	15	24
12	28.0–33.9	Yes	<1	31.6	Cesarean	Respiratory failure	Critical illness	232	14	18	22
13	28.0–33.9	Yes	>2	32.7	Cesarean	SROM and labor	Fetal heart rate	184	6	14	21
14	28.0–33.9	Yes	<1	30.7	Cesarean	Respiratory failure	Critical illness	62	14	25	28
15	28.0–33.9	No	NA	NA	NA	NA	NA	NA	0	1	7
16	28.0–33.9	Yes	>2	31.4	Cesarean	Respiratory failure	Critical illness	102	11	15	18
17	28.0–33.9	Yes	<1	30.1	Cesarean	Respiratory failure	Critical illness	576	9	9	13
18	28.0–33.9	Yes	<1	29.4	Cesarean	Respiratory failure	Critical illness	66	14	36	44
19	28.0–33.9	No	NA	NA	NA	NA	NA	NA	0	3	8
20	24.0–27.9	No	NA	NA	NA	NA	NA	NA	0	3	23
21	24.0–27.9	Yes	>2	30.0	Vaginal	SROM and labor	NA	161	14	29	38
22	24.0–27.9	No	NA	NA	NA	NA	NA	420	7	10	23
23	24.0–27.9	Yes	1–2	26.0	Cesarean	Fetal status	Fetal heart rate	92	10	12	13
24	24.0–27.9	No	NA	NA	NA	NA	NA	NA	13	15	21
25	24.0–27.9	No	NA	NA	NA	NA	NA	254	6	8	12
26	24.0–27.9	No	NA	NA	NA	NA	NA	183	14	41	61
27	24.0–27.9	Yes	>2	26.1	Cesarean	Fetal status	Fetal heart rate	417	8	21	38
28	24.0–27.9	No	NA	NA	NA	NA	NA	348	7	10	12
29	<24	No	NA	NA	NA	NA	NA	197	1	1	7
30	<24	No	NA	NA	NA	NA	NA	252	13	19	30
31	<24	No	NA	NA	NA	NA	NA	310	13	19	25
32	<24	No	NA	NA	NA	NA	NA	NA	0	2	5

Definition of abbreviations: COVID-19 = coronavirus disease; NA = not applicable; SROM = spontaneous rupture of membranes.

*Five patients were included as cases in References 4 and 5.

†The median ICU length of stay was 5 days (interquartile range [IQR], 2–12 d) for those without delivery versus 12 days (IQR, 5–21 d) for those who delivered during admission. The median hospital length of stay was 11 days (IQR, 6–22 d) for those without delivery versus 18 days (IQR, 8–28 d) for those who delivered during admission. The median duration of mechanical ventilation was 6 days (IQR, 0–13 d) for those without delivery versus 9 days (IQR, 1–14 d) for those who delivered during admission.

In summary, we report the maternal and fetal outcomes of 32 pregnant women in a multicenter cohort study of geographically diverse critically ill patients with COVID-19. In contrast to nonpregnant women of childbearing age, all pregnant women survived, and there were no fetal deaths. Treatments and outcomes, including receipt of invasive mechanical ventilation, the incidence of acute organ injury, and ICU and hospital length of stay, were generally similar between pregnant and nonpregnant women. Pregnant women had high rates of preterm delivery and cesarean section—primarily for the indication of critical illness. Our finding that 13 pregnant women survived to hospital discharge without delivery raises an interesting question of whether or not delivery is required for nonobstetric indications among critically ill pregnant women (10). Additional data are needed in critically ill pregnant women with COVID-19 to help inform clinical practice. ■

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What Sepsis Researchers Can Learn from COVID-19

To the Editor:

Despite intensive research efforts, the search for new therapeutic options for sepsis has yielded no result (1). However, the ongoing coronavirus disease (COVID-19) pandemic shows that effective therapeutic options for the distinct subgroup of viral sepsis due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can be found within months (2). What can sepsis researchers learn from the way COVID-19 is studied?

Heterogeneity

In clinical practice, recognition of the wider sepsis syndrome can improve awareness and timely initiation of treatment. However, when looking for new therapeutic options in a research setting, this broad approach may be less desirable. One of the questionable tenets of sepsis research has been whether the host response in sepsis represents a "final common pathway" irrespective of the source of infection or causative pathogens (1). This would justify looking at the broader sepsis population in research, with the added benefit of having larger study cohorts. However, most believe that the host response is just too complex and that a "final common pathway" may simply not exist (1). The resultant heterogeneity within the sepsis population is therefore considered to be a major limiting factor in finding specific sepsis therapies (1, 3). Extensive efforts have thus been made to reveal homogeneous sepsis subgroups (1, 3, 4).

Shared and distinct gene expression profiles are found when pulmonary and abdominal sepsis are compared (3), suggesting that part of the heterogeneity in the sepsis population could be explained by the infection site or invading pathogen. Several other studies that aim to find homogeneous sepsis subgroups through

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