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

Sarah Rae Easter, MD,[1] Shruti Gupta MD, MPH,[2] Samantha K. Brenner, MD, MPH,[3,4] David E. Leaf MD, MMSc[2]

[1]Divisions of Maternal Fetal Medicine and Critical Care Medicine and [2]Division of Renal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[3]Department of Internal Medicine, Hackensack Meridian School of Medicine at Seton Hall, Nutley, NJ

[4]Department of Internal Medicine, Heart and Vascular Hospital, Hackensack Meridian Health Hackensack University Medical Center, Hackensack, NJ

Corresponding Author:

Sarah Rae Easter, MD

75 Francis Street

Boston, Massachusetts 02115

seaster@bwh.harvard.edu

Phone: (804) 347-9167

Authorship Contributions: SRE, SG, and DEL 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. SRE, SKB, SG, and DEL wrote the manuscript. SRE performed the statistical analyses. SRE designed the tables. SRE, SG, SKB, and DEL acquired the data.
All authors provided feedback on the protocol and critically revised and approved the final version of the manuscript.

Funding & Disclosures: The authors are supported by the following grants from the National Institutes of Health: R01HL144566 (DEL); F32DC017342 (SG). DEL received research support from BioPorto unrelated to the current work. SG is a scientific coordinator for the ASCEND trial (GlaxoSmithKline).

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

Short Running Head: Critical Illness, Pregnancy, and COVID-19

Subject Category Descriptor: 4.6 ICU Management/Outcome

Letter Word count: 984

Impact Statement: Limited data are available on the clinical course of pregnant women with COVID-19 who require ICU care, particularly when compared to age-appropriate controls. Using data from a large, multicenter, geographically-diverse cohort of critically ill adults with laboratory-confirmed COVID-19 admitted to 67 hospitals across the United States, we report the clinical features of 32 pregnant and 64 non-pregnant women matched according to age and severity of illness. All pregnant women survived, and there were no fetal deaths, but pregnant women had high rates of preterm delivery and cesarean section.

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

To the Editor:

Data from viral respiratory illnesses such as influenza, SARS-CoV-1, and MERS suggest that pregnancy may worsen both maternal and fetal outcomes (1, 2). Existing data in critically ill pregnant women with COVID-19 are mainly limited to case series or systematic reviews lacking non-pregnant controls (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. Further, we compare the characteristics, treatment, and outcomes of these pregnant women to women who were not pregnant at the time of ICU admission.

We used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID), 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 non-pregnant women according to age (±2 years) and Quick Sequential Organ Failure Assessment (qSOFA) score on 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 until hospital discharge, death, or a minimum of 28 days after ICU admission. We compared outcomes between pregnant and non-pregnant women using chi-square or Fisher's exact test for categorical variables and the Wilcoxon Rank Sum test for continuous variables.

Among 4145 patients in the parent cohort, we identified 32 pregnant women and matched these to 64 non-pregnant women. The median age in both groups was 32 years (interquartile range [IQR], 27-35). In both groups, 62.5% of patients had a qSOFA score of 2 or 3 on admission. The frequency and severity of acute respiratory failure, assessed by receipt of invasive mechanical ventilation and the PaO_2/FiO_2 ratio on ICU admission, were similar between groups (**Table 1**).

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

Pregnant women were more likely to receive remdesivir (50.0% vs. 10.9%) and less likely to receive tocilizumab compared to non-pregnant women (9.4% vs. 23.4%). Receipt of invasive mechanical ventilation, prone positioning, and neuromuscular blockade during the 14 days following ICU admission was similar between groups. The incidence of venous thromboembolism and other acute organ injuries, along with ICU and hospital length of stay, was similar between groups (**Table 1**). There were no maternal or fetal deaths, whereas 6 of the 64 non-pregnant 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 less than 37 weeks' gestation. Only 3 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 non-reassuring fetal status (21.1%) (**Table 2**). A total of 17 of the 19 women (89.5%) who delivered were delivered by cesarean section, with maternal critical illness reported as the most common indication (41.2%). Among the 17 pregnant women with more than 30-weeks' gestation age at ICU admission, 15 (88.2%) were delivered, as compared to 4 out of 15 (26.7%) delivered with less than 30-weeks' gestational age.

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, we 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

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

known maternal hemodynamic and inflammatory burden accompanying major surgery such as cesarean section (8). Pregnant women in our cohort who were 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 compared to age- and qSOFA-matched non-pregnant 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.

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 non-pregnant 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 non-pregnant 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 non-obstetric indications among critically-ill pregnant women (10). Additional data are needed in critically ill pregnant women with COVID-19 to help inform clinical practice.

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

References

1. Callaghan WM, Creanga AA, Jamieson DJ. Pregnancy-related mortality resulting from influenza in the United States during the 2009-2010 pandemic. *Obstet Gynecol* 2015;126:486–490.

2.. Schwartz DA, Graham AL. Potential maternal and infant outcomes from coronavirus 2019-NCOV (SARS-CoV-2) infecting pregnant women: Lessons from SARS, MERS, and other human coronavirus infections. *Viruses* 2020;12:1–16.

3. Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effects of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcomes: a systematic review. *Ultrasound Obstet Gynecol*. 2020 Jul;56(1):15-27.

4. Pierce-Williams RAM, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, Penfield CA, Roman AS, DeBolt CA, Stone JL, Bianco A, Kern-Goldberger AR, Hirshberg A, Srinivas SK, Jayakumaran JS, Brandt JS, Anastasio H, Birsner M, O'Brien DS, Sedev HM, Dolin CD, Schnettler WT, Suhag A, Shabani Ahluwalia D, Reshama S. Navathe M, Adeeb Khalifeh M, Kathryn Anderson B, Vincenzo Berghella M. Clinical course of severe and critical COVID-19 in hospitalized pregnancies: a US cohort study. *Am J Obstet Gynecol MFM*. 2020 May 8;2(3). Online ahead of print.

5. Hirshberg A, Kern-Goldberger AR, Levine LD, Pierce-Williams R, Short WR, Parry S, Berghella V, Triebwasser JE, Srinivas SK. Care of critically ill pregnant patients with COVID-19: a case series. *Am J Obstet Gynecol*. 2020 May 8. Online ahead of print.

6. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava A, Zhou Y, Sutherland A, Green A, Shehata AM, Goyal N, Vijayan A, Velez JCQ, Shaefi S, Parikh CR, Arunthamakun J, Athavale AM, Friedman AN, Short SAP, Kibbelaar ZA, Omar SA,

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

Admon AJ, Donnelly JP, Gershengorn HB, Hernan MA, Semler MW, Leaf DE, STOP-COVID Investigators. Factors associated with death in critically ill patietns with coronavirus disease 2019 in the US. *JAMA Intern Med*. 2020 Jul 15. Online ahead of print.

7. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of Clinical Criteria for Sepsis For the Third International Concensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-74.

8. Jenkins TM, Troiano NH, Graves CR, Baird SM, Boehm FH. Mechanical ventilation in an obstetric population: characteristics and delivery rates. *Am J Obstet Gynecol*. 2003 Feb;188(2):549-52.

9. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, Seferovic MD, Aski SK, Arian SE, Pooransari P, Ghotbizadeh F, Aalipour S, Soleimani Z, Naemi M, Molaei B, Ahangari R, Salehi M, Oskoei AD, Pirozan P, Darkhaneh RF, Laki MG, Farani AK, Atrak S, Miri MM, Kouchek M, Shojaei S, Hadavand F, Keikha F, Hosseini MS, Borna S, Ariana S, Shariat M, *et al.* Maternal Death Due to COVID-19. *Am J Obstet Gynecol*. 2020 Jul;223(1):109.e1-109.e16.

10. Lapinsky SE, Rojas-Suarez JA, Crozier TM, Vasquez TM, Vasquez DN, Barrett N, Austin K, Plotnikow GA, Orellano K, Bourjeily G. Mechanical ventilation in critically-ill pregnant women: a case series. *Int J Obstet Anesth*. 2015 Nov;24(4):323-8.

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

Table 1. Characteristics, therapies, and outcomes according to pregnancy status

Characteristic	Pregnant (N=32)	Non-Pregnant (N=64)	p-value
Age (years) – median (IQR)	32 (27-35)	32 (27-35)	0.99
qSOFA score on ICU admission			0.99
0-1	12 (37.5)	24 (37.5)	
2-3	20 (62.5)	40 (62.5)	
Race – no. (%)			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 – no. (%)	9 (28.1)	20 (31.3)	0.75
Body mass index (kg/m^2) – median (IQR)[a]	33.7 (27.0-38.2)	36.7 (29.9-42.2)	0.10
Coexisting conditions – no. (%)			
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
Days from symptoms to ICU admission – median (IQR)	7 (5-10)		
Vital signs on day of ICU admission – median (IQR)			
Temperature – °C[a]	37.5 (37.0-38.0)	38.4 (37.3-39.3)	<0.01
Systolic blood pressure – mmHg	99 (91-110)	99 (89-106)	0.64
Heart rate – beats per min	116 (108-128)	119 (102-132)	0.81
Respiratory rate – breaths per min	28 (23-37)	34 (27-40)	0.02
Laboratory findings on day of ICU admission – median (IQR)[a]			
White blood cell count – per $\times 10^9$/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 (640-1374)	845 (441-1688)	0.68
C-reactive protein – mg/L	99 (77 - 118)	119 (53-237)	0.27
Invasive mechanical ventilation on ICU admission – no. (%)	18 (56.2)	37 (57.8)	0.88
PaO_2:FiO_2 , mm Hg – median (IQR)[a,b]	183 (108-261)	144 (100-230)	0.42
Gestational age at ICU admission, weeks – median (IQR)	30.4 (25.8-33.5)	NA	-
Treatments & Organ Injury within the first 14 days of ICU admission			
Interventions for hypoxemia – no. (%)			
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 – no. (%)			
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[c]	17 (53.1)	25 (39.1)	0.19
Therapeutic anticoagulation	13 (41.1)	28 (43.8)	0.77
Acute respiratory distress syndrome – no. (%)	16 (50.0)	16 (50)	0.03
Invasive mechanical ventilation – no. (%)	23 (71.9)	48 (75.0)	0.74
Days of mechanical ventilation – median (IQR)[b]	11 (6-14)	13 (8-14)	0.53
Vasopressors – no. (%)	23 (71.8)	23 (71.9)	0.23
Acute kidney injury – no. (%)[d]	4 (12.5)	15 (25.0)	0.16
Renal replacement therapy	0 (0)	6 (10.0)	0.09
Arrhythmia – no. (%)	1 (3.1)	1 (1.6)	0.99
Extra-corporeal membrane oxygenation – no. (%)	3 (9.4)	3 (4.7)	0.40
Thrombosis – no. (%)	2 (6.2)	7 (10.9)	0.71
Outcomes			
In-hospital death – no. (%)[e]	0 (0)	6 (9.4)	0.17
ICU length of stay, days – median (IQR)[e]	10 (3-18)	13 (5-24)	0.28
Hospital length of stay, days – median (IQR)[e]	14 (8-24)	11 (5-23)	0.13
Delivered during hospitalization – no. (%)[f]	19 (59.4)	NA	
Cesarean delivery – no. (%)[f]	17 (53.1)	NA	
Gestational age at delivery, weeks – median (IQR)	32.9 (30.1-34.4)	NA	

[a]Data were missing for creatinine for 3 non-pregnant patients, C-reactive protein for 10 pregnant and 21 non-pregnant patients, d-dimer for 8 pregnant and 29 non-pregnant patients, and PaO_2:FiO_2 for 10 pregnant and 11 non-pregnant mechanically ventilated patients.

[b]PaO_2/FiO_2 refers to the ratio of the partial pressure of arterial oxygen (PaO_2) over the fraction of inspired oxygen (FiO_2) and was only assessed in patients receiving invasive mechanical ventilation. Days of mechanical ventilation were limited to the first 14 days of hospitalization.

[c]Experimental therapies were remdesivir, tocilizumab, and convalescent plasma.

[d]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.

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

[e]In-hospital mortality data were available for all patients for a minimum of 28 days after ICU admission. Due to ongoing hospitalization, data on ICU length of stay data were incomplete for 14 patients, and data on hospital length of stay were incomplete for 24 patients.
[f]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).

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE

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

Case[a]	Gestational Age at ICU Admission (weeks)	Delivery During Admission	Gestational Age at Delivery (weeks)	Mode of Delivery	Indication for Delivery	Indication for Cesarean Delivery	PaO_2 to FiO_2 on Intubation	Duration of Mechanical Ventilation[b] (Days)	ICU Length of Stay[b] (Days)	Hospital Length of Stay[b] (Days)
1	40.7	Yes	40.6	Vaginal	Spontaneous labor	NA	513	1	1	5
2	36.4	Yes	36.4	Cesarean	Respiratory failure	Breech	NA	0	5	8
3	36.0	Yes	37.0	Cesarean	Fetal status	Fetal heart rate	NA	0	1	8
4	35.6	Yes	35.6	Cesarean	SROM[c]	Breech	268	6	7	13
5	34.7	Yes	34.3	Cesarean	Fetal status	Fetal heart rate	117	14	25	35
6	34.3	Yes	34.4	Cesarean	Respiratory failure	Critical illness	116	12	12	24
7	33.6	Yes	34.4	Cesarean	Preeclampsia	Critical illness	NA	0	1	4
8	33.6	Yes	33.6	Cesarean	Respiratory failure	Uterine surgery	NA	0	1	6
9	33.4	No	NA	NA	NA	NA	NA	0	1	3
10	33.4	Yes	33.4	Cesarean	Respiratory failure	Critical illness	101	5	6	14
11	32.6	Yes	32.9	Cesarean	Respiratory failure	Breech	158	14	15	24
12	31.6	Yes	31.6	Cesarean	Respiratory failure	Critical illness	232	14	18	22
13	31.3	Yes	32.7	Cesarean	SROM[c] & labor	Fetal heart rate	184	6	14	21
14	30.7	Yes	30.7	Cesarean	Respiratory failure	Critical illness	62	14	25	28
15	30.7	No	NA	NA	NA	NA	NA	0	1	7
16	30.6	Yes	31.4	Cesarean	Respiratory failure	Critical illness	102	11	15	18
17	30.1	Yes	30.1	Cesarean	Respiratory failure	Critical illness	576	9	9	13
18	29.4	Yes	29.4	Cesarean	Respiratory failure	Critical illness	66	14	36	44
19	28.4	No	NA	NA	NA	NA	NA	0	3	8
20	27.3	No	NA	NA	NA	NA	NA	0	3	23
21	26.1	Yes	30.0	Vaginal	SROM[c] & labor	NA	161	14	29	38
22	26.0	No	NA	NA	NA	NA	420	7	10	23
23	25.9	Yes	26.0	Cesarean	Fetal status	Fetal heart rate	92	10	12	13
24	25.9	No	NA	NA	NA	NA	NA	13	15	21
25	25.6	No	NA	NA	NA	NA	254	6	8	12
26	25.4	No	NA	NA	NA	NA	183	14	41	61
27	25.1	Yes	26.1	Cesarean	Fetal status	Fetal heart rate	417	8	21	38
28	24.9	No	NA	NA	NA	NA	348	7	10	12
29	23.9	No	NA	NA	NA	NA	197	1	1	7
30	23.1	No	NA	NA	NA	NA	252	13	19	30
31	19.3	No	NA	NA	NA	NA	310	13	19	25
32	18.1	No	NA	NA	NA	NA	NA	0	2	5

[a]Five patients were included as cases in references 4 and 5.
[b]Median ICU length of stay was 5 days (IQR, 2-12) for those without delivery versus 12 days (IQR, 5-21) for those delivered during admission. Median hospital length of stay was 11 days (IQR, 6-22) for those without delivery versus 18 days (IQR, 8-28) for those delivered during admission. Median days of mechanical ventilation was 6 days (IQR, 0-13) for those without delivery versus 9 days (IQR, 1-14) for those delivered during admission.
[c]SROM refers to spontaneous rupture of membranes.

AJRCCM Articles in Press. Published October 07, 2020 as 10.1164/rccm.202006-2182LE