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Perinatal outcomes in critically ill pregnant women with COVID-19

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Short title

COVID-19 critical care in pregnancy

AJOG at a glance

A. Why was this study conducted?
   - This study was conducted to characterize critical illness with COVID-19 in pregnancy and its effects on both mother and newborn.

B. What are the key findings?
   - Pregnant women manifested with varied symptoms, but all had multiple lab abnormalities in common
   - Pregnant women may indeed develop severe COVID-19 symptoms
   - Hispanic women may have a disproportionate incidence of critical illness.

C. What does this study add to what is already known?
   - Even with critical COVID-19, pregnant women may respond to the multimodal and multidisciplinary approach we describe.
   - Significant complications of prematurity in newborns can be expected as a result of critical COVID-19 in pregnancy, but vertical transmission was not identified.
   - Racial disparities may exist in pregnant women with critical illness

Keywords

COVID-19, pregnancy, critical care obstetrics, ARDS, critical care, ECMO

Objective

Early reports suggested pregnant women were not at increased risk for severe disease or death from COVID-19[1]. Few publications have described critical COVID-19 illness in pregnancy. This study describes the clinical characteristics and outcomes of critically ill mothers and their neonates within our health network since the onset of the COVID-19 pandemic in New Jersey.

Study Design

This IRB-approved, retrospective case series describes all pregnant women and their neonates requiring critical care for severe COVID-19 within our network's two largest hospitals in March and April 2020. Maternal demographic information, delivery method and indication, clinical symptomatology, imaging/laboratory findings, and treatment data were collected. Neonatal outcomes were also collected, including real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2.

Results

There were 1,053 deliveries between both hospitals during the study period, with 73 (6.9%) documented symptomatic COVID-19 positive pregnant patients. Of these, 31 (42%) were admitted for management of COVID-19 symptoms. Eight (26%) of those admitted required intensive care unit (ICU) admission, 6 (19%) required intubation, and 1 (3.2%) was supported with extracorporeal membrane oxygenation (ECMO). Therefore, 8 (11%) of the 73 symptomatic positive cases developed critical illness.

Table 1 describes the maternal demographics, clinical characteristics and treatments of the 8 critical care patients treated during the study period. Mean age and BMI were 30.5±9.0 years and 34±7.9 kg/m^2 respectively. Median gravidity and parity were 2.5(3.5) and 1(2.75). Mean gestational age at presentation was 30.6 weeks and mean gestational age at delivery was 31.4 weeks. Notably, 7 of the women (87.5%) were Hispanic, despite the two health centers having Hispanic populations of 24.7% and 8%, respectively. Two women had pre-existing conditions (chronic hypertension, asthma), and one presented with HELLP syndrome. Seven (87.5%) were delivered preterm by primary cesarean delivery; one remains undelivered.

Five of the eight critical patients had an oxygen saturation less than 94% on admission. Only 1 was febrile on admission, though 5 (62.5%) developed fever during hospitalization. Most had cough (75%) and dyspnea (87.5%). All had elevated transaminases and D-dimer levels. C-reactive protein (CRP), lactate dehydrogenase (LDH), and Interleukin-6 levels were elevated in all women who received those tests.

Treatments are summarized in Supplemental Figure 1. All required oxygen supplementation; most received a combination of medical interventions. Six (75%) required intubation and one (12.5%) received venovenous ECMO for 12 days. Three women required norepinephrine and prone positioning, which was accomplished after delivery. All women were discharged in stable condition.

Patients 1 through 8 in Table 1 pair with neonates 1 through 8 (Patient/Neonate 5 remains undelivered) in Supplemental Table 2. All neonates were premature and required NICU admission. Respiratory distress was universal and predominantly severe (85.7%). Neonatal morbidities were significant. All tested negative by RT-PCR for SARS-CoV-2.

Conclusion

Our case series illustrates the potential severity of COVID-19 in pregnant women and provides a model of management that may be useful for obstetric providers. Most women in our series were Hispanic, which is disproportionately high given the demographics of our institutions. Information on other social determinants of health was not available. This finding warrants further investigation considering emerging racial disparities of COVID-19 related deaths[2]. Most women had rapid onset of disease, developed severe hypoxia, and had significant findings on lung imaging. Fever on initial presentation was uncommon. All had elevation of liver transaminases, CRP and D-dimer.

There are conflicting data on the risk for preterm delivery associated with COVID-19 in pregnancy[3, 4]. Seven of the eight women with critical respiratory illness in our series required preterm delivery with the goal of reducing respiratory compromise by decreasing oxygen requirements and enhancing diaphragmatic excursion[5, 6]. Antenatal corticosteroids were not given universally because of the theoretic potential to exacerbate COVID-19 infection and pulmonary edema. Rapid deterioration was another limiting factor.

All women were discharged home in good health following a multimodal, multidisciplinary approach including intubation, prompt delivery, off-label use of experimental therapies (e.g. remdesivir, convalescent plasma), and even ECMO. While there was a significant burden of prematurity, each neonate improved as expected with NICU care and there was no evidence of vertical transmission.

Obstetric providers should be aware of the potential for critical COVID-19 illness in pregnancy. Without clear guidelines for treatment, providers are left with unproven

therapies without sufficient safety data, and while treatment was ultimately successful in all patients, it is impossible to state whether any individual intervention is an improvement over standard supportive care. As research evolves during this crisis, management options will be clarified. Providers should recognize clinical deterioration in pregnant women and intervene swiftly to limit maternal and fetal harm.

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123 Table 1. Description of eight critically ill COVID-19 pregnant women requiring intensive care

Patient number	1	2	3	4	5	6	7	8
Demographic information								
Age	41	21	36	32	43	26	19	26
Gravidity/parity	G3P2	G1P0	G2P0	G5P3	G5P3	G2P0	G1P0	G4P2
BMI (kg/m^2)	49	27	26	36	36	33	26	39
Race/ethnicity	Hispanic	Hispanic	Asian	Hispanic	Hispanic	Hispanic	Hispanic	Hispanic
Gestational age at presentation (weeks)	30 5/7	33 0/7	35 0/7	30 0/7	26w4d	27 6/7	31 1/7	30 1/7
Gestational age at delivery (weeks)	30 5/7	33 3/7	35 0/7	30 1/7	Undelivered	28 1/7	31 6/7	30 2/7
Medical/obstetric	Chronic	None	None	Asthma	None	None	Preeclampsia	None

comorbidities	hypertension, hypothyroidism							
Delivery method	Primary CD with tubal ligation	Primary CD	Primary CD	Primary CD	Undelivered	Primary CD	Primary CD	Primary CD
Reason for CD	Respiratory failure	Respiratory failure	Respiratory failure	Respiratory failure	N/A	Respiratory failure	HELLP	Respiratory failure
Clinical Data, On Admission (maximum)								
Oxygen saturation	78%	93%	93%	97%	96%	93%	98%	87%
Temperature (°F), presentation (Tmax)	98.9 (100.9)	97.6 (100)	100.1 (100.5)	101.4 (101.4)	100.3 (100.3)	99 (101.6)	97.6 (100.2)	98.3 (101.5)

Cough	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Dyspnea	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Chest x-ray/CT findings	Severe diffuse interstitial and airspace disease	Patchy peripheral bilateral lung opacities	Patchy bilateral lower lung infiltrates	Moderate patchy bilateral airspace disease	Low lung volumes, patchy bilateral infiltrates	Left upper lobe and right lower lobe opacities	Negative	Bilateral opacities consistent with pneumonia
Ferritin (ng/ml)	510 (540)	487 (487)	1,118 (1,899)	57.6 (91)	64 (114)	192 (218)	437 (437)	183 (183)
AST (U/L)	73 (84)	300 (300)	23 (117)	30(107)	35 (44)	50 (99)	20 (1343)	76 (76)
ALT (U/L)	27 (49)	248 (248)	26 (95)	14 (74)	18 (18)	35 (45)	6 (246)	79 (79)
D-dimer (μg/mL)	2.7 (2.7)	1.6 (2.9)	1.3 (1.3)	1.1 (3.3)	0.96 (1.1)	0.93 (1.4)	26 (46.3)	0.94 (6.2)

WBC (x10^3 cells/mL)	6.3 (14.8)	3.6 (15.5)	7.5 (10.5)	5.9 (16.8)	11 (18)	5.4 (12)	10.6 (20.6)	3.9 (17.7)
Absolute lymphocytes (cells/mcL)	720	670	2,380	1620	900	700	2600	400
Platelets (x10^3 cells/mL)	229 (413)	110 (508)	269 (469)	169 (376)	344 (774)	129 (379)	280 (322)	121 (223)
C-reactive protein (mg/dL)	7.8 (14.3)	6.0 (11.9)	14.2 (17.7)	10.6 (13.0)	17.4 (24.3)	0.56 (0.56)	23.6 (23.6)	16.8 (16.8)
LDH (U/L)	524 (1,042)	379 (465)	268 (432)	261 (568)	226 (386)	222 (222)	172 (1,785)	257 (403)
Il-6 (pg/mL)	7 (138)	<5 (39)	24 (45)	6 (441)	17 (17)	N/A	N/A	N/A
Standard and Critical Care Treatments								
Antenatal	No	Yes	No	No	No	Yes	Yes	Yes

corticosteroids								
Supplemental O_2 by nasal cannula	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hydroxychloroquine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Azithromycin	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Ascorbic acid	Yes	Yes	No	Yes	No	Yes	No	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes	No	No	No
Ceftriaxone	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Convalescent plasma	No	Yes	No	No	Yes	No	No	No
Intubation	Yes	Yes	Yes	Yes	No	Yes	No	Yes

Prone positioning	Yes	Yes	No	No	No	Yes	No	No
Tocilizumab	Yes	Yes	No	Yes	No	Yes	No	Yes
Remdesivir	Yes	Yes	Yes	Yes	No	No	No	Yes
Heparin/enoxaparin (prophylactic)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Vasopressor (norepinephrine)	Yes	Yes	No	Yes	No	No	No	No
VV ECMO	Yes	No	No	No	No	No	No	No

BMI=body mass index, CD=cesarean delivery, HELLP=hemolysis elevated liver enzymes and low platelets syndrome, AST=aspartate aminotransferase, ALT=alanine aminotransferase, WBC=white blood cell count, LDH=lactate dehydrogenase, VV ECMO=venovenous extracorporeal membrane oxygenation

Table 2. Characteristics, treatments and outcomes of seven neonates born to COVID-19 positive mothers

Neonate	1	2	3	4	5 (un-delivered)	6	7	8
Maternal labor	No	No	No	No		No	No	No
Length of rupture of membranes	At delivery	At delivery	At delivery	At delivery		At delivery	At delivery	At delivery
Category II or III fetal heart tracing	No	No	No	No		No	No	No
Gestational age (weeks)	30 5/7	33 3/7	35 0/7	30 1/7		28 1/7	31 6/7	30 2/7
Birth weight (g), Size category	1400, AGA	2410, AGA	2680, AGA	1530, AGA		1250, AGA	1310, SGA	1710, AGA
Antenatal	No	Yes	No	No		Yes	Yes	Yes

corticosteroids								
Sex	Female	Male	Female	Female		Male	Female	Male
Apgar score (1, 5,10 min)	1, 4	3, 4, 9	7, 9	7, 8		1, 7	3, 5, 7	4, 9
Resuscitation	O2, CPAP, PPV, intubation, surfactant	O2, CPAP, PPV, intubation	O2, CPAP, PPV	O2, CPAP		CPAP, PPV	O2, CPAP, PPV, intubation	CPAP, PPV, intubation, surfactant, tracheal suctioning
Separated immediately after delivery	Yes	Yes	Yes	Yes		Yes	Yes	Yes
Length of stay (days)	39	15	7	34+		35+	13+	16+
Final disposition	Home	Home	Home	Remains hospitalized		Remains hospitalized	Remains hospitalized	Remains hospitalize

								d
Respiratory distress present	Yes, RDS	Yes, RDS	Yes, TTN	Yes, RDS		Yes, RDS	Yes, RDS	Yes, RDS
Respiratory support required	Mechanical ventilation, CPAP, HHFNC	Mechanical ventilation, CPAP, HHFNC	CPAP	Mechanical ventilation, CPAP, HHFNC		Mechanical ventilation, CPAP, HHFNC	Mechanical ventilation, CPAP, HHFNC	Mechanical ventilation, CPAP, HHFNC
Lowest leukocyte count in first 7 days ($x10^3$/mcL)	5.5	6.3	13.7	8.3		8.6	9.1	10.3
Lowest neutrophil count in first 7 days ($x10^3$/mcL)	1.54	2.74		2.7		4.6	6.4	6.0

Lowest lymphocyte count in first 7 days ($x10^3$/mcL)	3.36	2.62		4.89		3.6	3.8	2.4
Lowest hemoglobin in first 7 days (g/dL)	14.7	16.6	17.6	14.4		11.5	18.5	19.4
Highest C-reactive protein in first 7 days (mg/dL)	0.55		0.08			0.11		
Other neonatal morbidities	Apnea, hyperbilirub	Hyperbiliru binemia of	Hyperbiliru binemia of	Apnea, hyperbilirub		Apnea, hyperbilirubi	Apnea, hyperbilirubi	Apnea of prematurit

	inemia of prematurity, feeding problems, temperature instability, observation and evaluation for sepsis	prematurity, feeding problems, temperature instability	prematurity, extralobar pulmonary sequestration, observation and evaluation for sepsis, feeding problems	inemia of prematurity, feeding problems, temperature instability, IVH		nemia of prematurity, anemia of prematurity, NEC, temperature instability	nemia of prematurity, temperature instability, feeding problems	y, temperature instability, feeding problems
Treatments administered	Antibiotics for 48 hr, TPN, surfactant, caffeine,	TPN, phototherapy	Intravenous fluids, antibiotics for 48 hr, phototherap	TPN, surfactant, caffeine, phototherapy		Antibiotics for 48 hr, TPN, surfactant, caffeine, phototherapy	TPN, caffeine, phototherapy	TPN, caffeine, surfactant

	phototherapy		y					
Head Ultrasound Results	Normal, day of life 7			Unilateral grade 1 IVH on day of life 8		Normal, day of life 5	Normal, day of life 2	Normal, day of life 5
SARS-CoV-2 RT-PCR testing done	Yes	Yes	Yes	Yes		Yes	Yes	Yes
Specimen type, timing and result	NP at 24 hr and 7 days	NP at 24 hr	NP at 24 hr and 7 days	NP at 24 hr and 7 days		NP at 24 hr, 72 hr and 10 days	NP at 48 hr and 72 hr	NP at 48 hr and 72 hr
COVID-19 test result(s)	Negative	Negative	Negative	Negative		Negative	Negative	Negative
Type of Feeding Provided and	Formula, no maternal	Formula	Formula, no maternal	Donor breast milk,		Donor breast milk	Donor breast milk	Expressed maternal

Feeding Method	breast milk		breast milk	no maternal breast milk				and donor breast milk
Discharge	Discharged to father (SARS-CoV-2 neg)	Discharged to father (SARS-CoV-2 neg)	Discharged to father (PUI)	Remains hospitalized		Remains hospitalized	Remains hospitalized	Remains hospitalized

AGA=appropriate for gestational age, SGA=small for gestational age, CPAP=continuous positive airway pressure, PPV=positive pressure ventilation, NICU=neonatal intensive care unit, RDS=respiratory distress syndrome, TTN=transient tachypnea of the newborn, HHFNC=humidified high flow nasal cannula, NEC=necrotizing enterocolitis, TPN=total parenteral nutrition, RT-PCR=real time polymerase chain reaction, NP=nasopharyngeal

Figure captions

Figure 1. Treatments received by 8 critical care COVID-19 pregnant patients