


Clinical Stratification of Pregnant COVID-19 Patients based on Severity: A Single Academic Center Experience

Marissa Berry, MD¹ Amanda Wang, MD¹ Shannon M. Clark, MD¹ Hassan M. Harirah, MD¹
 Sangeeta Jain, MD¹ Gayle L. Olson, MD¹ Luis D. Pacheco, MD¹ George R. Saade, MD¹
 Antonio F. Saad, MD¹ 

¹ Division of Maternal-Fetal Medicine, The University of Texas Medical Branch, Galveston, Texas

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Address for correspondence Antonio F. Saad, MD, Department of Obstetrics and Gynecology, Critical Care Medicine & Maternal Fetal Medicine, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0587 (e-mail: afsaad@utmb.edu).

Abstract

Objective This study aimed to describe baseline characteristics of a cohort of pregnant women infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and determine if these correlate with disease severity and perinatal outcomes.

Study Design This was a retrospective cohort trial conducted at the University of Texas Medical Branch Galveston, Texas. All pregnant women presented to our medical center, who were screened and tested positive for SARS-CoV-2 virus, were included. We stratified our study population in three groups: asymptomatic, symptomatic not requiring oxygen therapy, and patients requiring oxygen support to maintain oxygen saturation >94%. Relevant population characteristics, laboratory data, and maternal and neonatal outcomes were abstracted. A p -value <0.05 was considered statistically significant.

Results Between March and July 2020, 91 women tested positive for SARS-CoV-2 upon admission to our labor and delivery unit. Among these, 61.5% were asymptomatic, 34.1% were symptomatic, and 4.4% required oxygen support. Our population was mainly Hispanic (80.2%), multiparous (76.9%), obese (70.3%), and with a median age of 27 years. Median gestational age at symptom onset or diagnosis was 36 weeks. Significant differences were found between gestational age and disease severity. Maternal characteristics including age, body mass index (BMI), and presence of comorbid conditions did not appear to influence severity of SARS-CoV-2 infection. Significant laboratory findings associated with increasing disease severity included decreasing hemoglobin and white blood cell count, lymphopenia, and increasing levels of inflammatory markers including CRP, ferritin, and procalcitonin. Maternal and neonatal outcomes did not differ among groups. No SARS-CoV-2 was detected by polymerase chain reaction testing in neonates of mothers with COVID-19.

Conclusion Pregnant patients with COVID-19 infection are predominantly asymptomatic. Patients appear to be at increased risk for more severe infection requiring oxygen support later in pregnancy.

Keywords

- COVID-19
- pregnancy
- severity
- characteristics
- outcomes

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Key Points

- The majority of pregnant patients with COVID-19 are asymptomatic and <1 in 20 require oxygen support.
- Women in the later stages of pregnancy may be at increased risk for severe infection.
- Anemia, leukopenia, CRP, ferritin, and procalcitonin are associated with increasing severity.

Initial reports of coronavirus disease 2019 (COVID-19) as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus began to emerge in Wuhan, China in late 2019; a global pandemic was declared by March 2020. Global cases now exceeded 16 million, with greater than 4 million reported in the United States.^{1,2} With the rise of COVID-19 cases in the United States, there has been an increasing impact on special populations, including pregnant patients.

We have recently implemented a universal screening policy in our obstetrical units, allowing us a unique opportunity for the identification of both asymptomatic and symptomatic patients. Despite the fact that most pregnant patients diagnosed with COVID-19 are asymptomatic,^{3,4} pregnancy appears to increase the risk for hospitalization, intensive care unit (ICU) admission, and need for mechanical ventilation.² While cases of maternal death due to COVID-19 have been reported, infected pregnant patients are not thought to be at increased risk of death compared with nonpregnant individuals.^{2,5}

Published data on the association between baseline patient characteristic and COVID-19 severity are mixed.^{3,4,6,7}

The purpose of this study was to describe baseline characteristics of a cohort of pregnant women infected with SARS-CoV-2 and determine if these correlate with disease severity and perinatal outcomes.

Materials and Methods

This was a single-center retrospective cohort trial. The institutional review board (IRB) approved the protocol.

All pregnant women who were admitted to our labor and delivery unit with confirmed SARS-CoV-2 infection between March 2020 and July 2020 were included in the study. During this period, universal screening for COVID-19 was performed in our institution. Nasopharyngeal swab samples were attained by trained nursing staff wearing appropriate personal protective equipment (PPE) according to current guidelines. Detection of SARS-CoV-2 virus was performed by using the Abbott ID NOW COVID 19 (Abbott Diagnostics Scarborough, Inc., Scarborough, ME) or Xpert Xpress SARS-CoV-2 (Cepheid Sunnyvale, CA). The real time-PCR was completed according to the manufacturer's protocol. Results were reported less than 1 hour from sample collection as "positive," "negative," or "invalid." Negative and positive results were reported in the medical records and used to guide medical staff in clinical management of patients as per our institution's established protocols. Invalid results were handled as per standard laboratory protocol in our center and consisted mainly of resampling and repeating the test.

We first stratified our population by three groups: asymptomatic, symptomatic but not requiring oxygen support, and patients requiring oxygen support to maintain oxygen saturation >94%. Applicable population characteristics and laboratory data were abstracted. We also collected relevant maternal and neonatal outcomes. A composite of NICU admission, respiratory support, hypoxic ischemic encephalopathy, seizures, sepsis, meconium aspiration syndrome, birth trauma, intracranial or subgaleal hemorrhage, hypotension requiring pressors, and perinatal death was used to evaluate perinatal outcomes.

Statistical analyses were performed by using STATA 16 software (StataCorp, College Station, TX). Normality was performed by using the Shapiro–Wilk test. Chi-square or Fisher exact test were used for categorical data and Kruskal–Wallis test was used for continuous variables as appropriate. A *p*-value <0.05 was considered statically significant.

Results

A total of 91 women were tested positive for SARS-CoV-2 virus during the study period with a positivity rate close to 3%. Our population was mainly young (median age = 27), Hispanic (80.2%), multiparous (76.9%), and obese (BMI > 30; 70.3%) (→Table 1). Median gestational age at symptom onset or diagnosis was 36 weeks. Among these, 44% had a positive screening questionnaire at the time of evaluation. In total, 35 (38%) were symptomatic and only four (4.4%) required oxygen support (→Table 1). Oxygen support was provided initially by conventional nasal cannula, oxygen mask, and converted ultimately to high-flow nasal cannula with a goal of oxygen saturation >94%. The three most common presenting symptoms were cough, fever, and shortness of breath (→Table 1). Delivery was dictated by obstetric indications in 100% of asymptomatic and symptomatic patients not requiring oxygen therapy, and in 66.7% of those requiring oxygen support. One patient requiring oxygen support was delivered due to worsening respiratory status. Vaginal delivery rates were 57.1% among asymptomatic patients, 66.7% in symptomatic patients, and 33.3% in those requiring oxygen support. Cesarean section was performed for an obstetric indication in 98.9% of patients. The preterm delivery rate was 9.9% (→Table 1).

There was a significant association between gestational age and COVID-19 severity. Median gestational age was 37 weeks in asymptomatic patients, 33 weeks in symptomatic patients, and 36 weeks in patients requiring oxygen support (*p* = 0.01). There were no differences noted between severity and maternal characteristics including age, parity, BMI, and race/ethnicity. Household exposures were identified significantly more frequently in symptomatic patients and in those requiring oxygen support (*p* = 0.01).

Table 1 Severe acute respiratory syndrome coronavirus 2 positive population characteristics stratified by severity

Maternal characteristics	Asymptomatic (n = 56)	Symptomatic (n = 31)	Oxygen support ^{tt} (n = 4)	p-Value ^a
Age	27 (16–43)	26 (15–38)	35 (29–37)	0.41
Gestational age (wk) at symptoms	37 (17–40)	33 (14–40)	36 (27–38)	0.01
Gestational age (wk) at deliver	39 (27–40)	39 (30–40)	37 (36–38)	0.16
Gravidity	3 (1–11)	3 (1–7)	3 (2–5)	0.64
Parity	2 (0–6)	1 (0–4)	1 (0–3)	0.40
Symptom onset to clinical evaluation (days)		2 (0–14)	2 (0–3)	0.53
BMI	32 (20–61)	31 (19–47)	33 (31–75)	0.59
BMI ≥ 30 kg/m ²	42 (75%)	18 (58.06%)	4 (100%)	0.128
Race				0.06
White	47 (83.93%)	29 (93.55%)	2 (50%)	
African American	9 (16.07%)	2 (6.45%)	2 (50%)	
Hispanic	45 (80.3%)	26 (83.87%)	2 (50%)	0.27
Health care workers	2 (3.57%)	0 (0%)	0 (0%)	0.57
Medical comorbidities				0.08
None	35 (62.5%)	21 (67.7%)	2 (50%)	
Asthma	0 (0%)	2 (6.45%)	0 (0%)	
Preeclampsia	8 (14.29%)	0 (0%)	1 (25%)	
Chronic hypertension	3 (5.36%)	0 (0%)	1 (25%)	
Gestational diabetes	1 (1.79%)	1 (3.23%)	0 (0%)	
Pregestational diabetes	2 (3.57%)	1 (3.23%)	0 (0%)	
One or more	2 (3.57%)	4 (12.9%)	0 (0%)	
Other	5 (8.93%)	2 (6.45%)	0 (0%)	
Type of exposure				0.01
Unidentified	50 (89.29%)	22 (70.97%)	3 (75%)	
Household	1 (1.79%)	8 (25.81%)	1 (25%)	
Community	3 (5.36%)	1 (3.23%)	0 (0%)	
OCC	2 (3.57%)	0 (0%)	0 (0%)	
Prior + COVID test	10 (17.86%)	4 (12.90%)	1 (25%)	0.61
Fever	0 (0%)	11 (35.48%)	1 (25%)	<0.0001
Myalgia	0 (0%)	6 (19.35%)	1 (25%)	0.002
Malaise	0 (0%)	5 (16.13%)	1 (25%)	0.002
Chills/rigor	0 (0%)	5 (16.67%)	0 (0%)	0.006
Cough	0 (0%)	12 (38.71%)	2 (50%)	<0.0001
Headache	0 (0%)	3 (9.68%)	0 (0%)	0.06
Shortness of breath	0 (0%)	6 (19.35%)	2 (50%)	<0.0001
Runny nose	0 (0%)	1 (3.23%)	0 (0%)	0.385
Sore throat	0 (0%)	6 (19.35%)	0 (0%)	0.01
Diarrhea	0 (0%)	3 (9.68%)	0 (0%)	0.05
Chest pain	0 (0%)	4 (12.9%)	0 (0%)	0.02
+ CDC screening questionnaire	7 (12.50%)	29 (93.55%)	4 (100%)	<0.0001
Anemia ^b	12 (28.58%)	11 (42.31%)	3 (75%)	0.117
Leukocytosis ^c	7 (16.67%)	2 (7.69%)	0 (0%)	0.586
Lymphopenia ^d	8 (19.05%)	13 (50%)	4 (100%)	0.001
Thrombocytopenia ^e	5 (11.9%)	4 (15.38%)	1 (25%)	0.517
Elevated BUN ^f	0 (0%)	1 (8.33%)	0 (0%)	1
Elevated Creatinine ^g	0 (0%)	1 (7.14%)	0 (0%)	0.486

(Continued)

Table 1 (Continued)

Maternal characteristics	Asymptomatic (n = 56)	Symptomatic (n = 31)	Oxygen supportt (n = 4)	p-Value ^a
Acute kidney injury	0 (0%)	1 (4.76%)	0 (0%)	
Elevated AST ^h	4 (25%)	3 (23.08%)	2 (50%)	0.74
Elevated ALT ⁱ	6 (37.50%)	1 (7.69%)	0 (0%)	0.109
Abnormal chest X-ray or CT	0	4 (40%)	4 (100%)	0.08
+ Rapid SARS-CoV-2 PCR	51 (94.44%)	28 (96.55%)	4 (100%)	1
+ Nucleic acid SARS-CoV-2 PCR	8	5	0 (0%)	N/A
+ SARS-CoV-2 IgG	11	2	1	N/A
Administration of antibiotics	0 (0%)	1 (3.23%)	2 (50%)	0.002
Administration of antiretrovirals	0 (0%)	0 (0%)	3 (75%)	<0.0001
Dexamethasone	0 (0%)	0 (0%)	2 (50%)	0.001
Methyl prednisolone	0 (0%)	0 (0%)	1 (25%)	0.044
ICU admission	0 (0%)	0 (0%)	3 (75%)	<0.0001
Invasive mechanical ventilation	0 (0%)	0 (0%)	0 (0%)	
Nasal cannula	0 (0%)	0 (0%)	4 (100%)	<0.0001
Face mask	0 (0%)	0 (0%)	2 (50%)	0.001
High-flow nasal cannula	0 (0%)	0 (0%)	4 (100%)	<0.0001
Ongoing pregnancy	14 (25%)	16 (51.61%)	1 (25%)	0.04
Indication for delivery				0.05
Obstetric	42 (100%)	15 (100%)	2 (66.67%)	
COVID	0 (0%)	0 (0%)	1 (33.33%)	
Delivery < 37 wk	5 (11.9%)	3 (20%)	1 (33.33%)	0.33
Stillbirth	1 (2.38%)	0 (0%)	0 (0%)	1
Vaginal delivery	24 (57.14%)	7 (66.67%)	1 (33.33%)	0.58
Indication for cesarean				0.345
Obstetric	19 (100%)	7 (87.50%)	2 (100%)	
COVID	0 (0%)	1 (12.50%)	0 (0%)	
Postpartum hemorrhage	3 (7.14%)	1 (6.67%)	1 (33.33%)	0.316
Hospital duration (d)	1 (0–7)	1 (0–12)	7 (6–12)	0.1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CDC, Centers for Disease Control and Prevention; CRP, C-reactive protein; OCC, Office of the Comptroller of the Currency; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Note: Data are presented as *n* (%) or median (range).

^aKruskal–Wallis test; Pearson's Chi-square test or Fisher's exact.

^b< 11 g/dL in first and third trimesters and <10.5 g/dL in second trimester.

^cWhite blood count > 11.1 $\times 10^3/\mu\text{L}$.

^dLymphocyte count < 1.32 $\times 10^3/\mu\text{L}$.

^ePlatelet count < 150 $\times 10^3/\mu\text{L}$.

^fBUN > 23 mg/dL.

^gCreatinine > 1.04 mg/dL.

^hAST > 40 U/L.

ⁱALT > 35 U/L.

Laboratory findings significantly associated with increasing severity of disease included anemia ($p=0.01$), leukopenia ($p<0.01$), lymphopenia ($p<0.01$), elevated CRP ($p=0.01$), elevated ferritin ($p=0.03$), and elevated procalcitonin ($p=0.02$) (→Table 2).

Composite neonatal outcomes did not differ among groups (→Table 3). The rate of NICU admission was 29.7%. One patient presented for the management of intrauterine fetal demise and was found to be COVID-19 positive and asymptomatic. The patient opted for autopsy of the fetus,

which determined the intrauterine demise was likely secondary to an umbilical cord accident. All neonates tested negative for SARS-CoV-2 via RT-PCR at 24 hours of life.

Discussion

Universal testing in labor and delivery has allowed us to demonstrate a range of severity of COVID-19 in pregnant women. Of those who tested positive, the majority were asymptomatic patients presenting for either scheduled delivery

Table 2 Maternal laboratory findings at admission

Laboratory Components	Asymptomatic	Symptomatic	Oxygen Support	p-Value ^a
Hemoglobin (11.0–15.0 g/dL)	11.8 (6.4–13.1)	11.2 (8.3–14)	10.9 (7.7–12.2)	0.01
White blood count ($4.3\text{--}11.1 \times 10^3/\mu\text{L}$)	8.4 (5.4–16.1)	7.5 (3.8–14.2)	4.8 (4.6–6.1)	0.004
Lymphocyte ($1.32\text{--}3.29 \times 10^3/\mu\text{L}$)	1.67 (0.7–3.5)	1.29 (0.6–3.5)	0.8 (0.5–0.89)	0.0007
Platelets ($150\text{--}358 \times 10^3/\mu\text{L}$)	203 (88–409)	224 (108–347)	150 (144–235)	0.68
BUN (7–23 mg/dL)	5 (4–7)	4 (2–50)	8 (4–9)	0.72
Creatinine (0.5–1.04 mg/dL)	0.5 (0.26–0.91)	0.42 (0.26–2.5)	0.57 (0.37–0.72)	0.48
AST (13–40 U/L)	30 (21–73)	37 (19–54)	37 (32–54)	0.98
ALT (5–35 U/L)	18 (9–122)	17 (8–38)	18 (12–25)	0.21
CRP (<0.8 mg/dL)	0.3 (0.1–3.6)	2.7 (0.8–4.2)	8.1 (1.2–10.3)	0.01
Ferritin (6.0–137.0 ng/mL)	15.2 (7.6–23)	24 (11.6–150)	71 (18–138)	0.03
Procalcitonin (<0.07 ng/mL)	0.02 (0.02–0.04)	0.05 (0.02–0.14)	0.63 (0.17–0.67)	0.02
D-Dimer (<0.5 $\mu\text{g/mL}$)	1.38 (1.31–1.46)	1.96 (0.65–3.38)	1.65 (0.87–5.58)	0.28
LDH (300–600 U/L)	484 (339–1,134)	432 (308–734)	629 (516–1,515)	0.88

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin.

Note: Data are presented as median (range).

^aKruskal–Wallis test; Pearson's Chi-square test or Fisher's exact.

Table 3 Perinatal characteristics and outcomes

Neonatal characteristics	Asymptomatic (n = 42)	Symptomatic (n = 15)	Oxygen support (n = 3)	p-Value ^a
Birthweight in grams	3,185 (570–4,410)	3,145 (1,050–3,710)	3,480 (2,540–3,500)	0.95
Arterial cord pH < 7.2	2 (6.45%)	3 (27.27%)	0 (0%)	0.2
Apgar's score at 1 min	8 (0–9)	8 (7–9)	8 (8–8)	0.62
Apgar's score at 5 min	9 (0–9)	9 (8–9)	9 (9–9)	0.93
+ COVID PCR	0 (0%)	0 (0%)	0 (0%)	NA
Perinatal death	1 (2.33%)	0 (0%)	0 (0%)	1
Respiratory support	8 (19.05%)	4 (26.67%)	1 (3.33%)	0.64
HIE	0 (0%)	0 (0%)	0 (0%)	NA
Seizures	0 (0%)	0 (0%)	0 (0%)	NA
Sepsis	0 (0%)	0 (0%)	0 (0%)	NA
NICU admission	18 (42.86%)	7 (46.67%)	2 (66.67%)	0.8
Hypotension requiring pressors	0 (0%)	0 (0%)	0 (0%)	NA
Intracranial or subgaleal hemorrhage	1 (2.38%)	0 (0%)	0 (0%)	1
Neonatal composite	20 (47.62%)	7 (46.67%)	2 (66.67%)	0.91

Abbreviations: HIE, hypoxic-ischemic encephalopathy; NA, not applicable; NICU, neonatal intensive care unit; PCR, polymerase chain reaction.

Note: Data are presented as n (%) or median (range).

^aKruskal–Wallis test; Pearson's Chi-square test or Fisher's exact.

or an obstetric complaint. Identifying asymptomatic patients has provided more information on the epidemiology and clinical course of the infection. It has also allowed staff members to take appropriate precautions against transmission, especially during aerosolizing events including the second stage of labor or perioperative endotracheal intubation.

The testing algorithm on labor and delivery at our institution is to initially test all patients using the Abbott ID NOW Rapid test. If this test is negative and suspicion of infection remains (e.g., presence of symptoms), then the molecular nucleic acid RT-PCR test is performed. Studies have demonstrated a wide range in

the false negative rate of the Abbott ID NOW, one reporting 6.3% and another between 33 and 45%.^{8,9} In our cohort, four symptomatic patients had a negative rapid screen followed by a positive nucleic acid RT-PCR test. As follow-up testing was not routinely performed for asymptomatic individuals, our true false negative rate is unknown. While false negative tests were not commonly identified in our cohort, the possibility of false negative screening tests must be recognized.

With the data collected, we noted demographics, clinical characteristics, and maternal and neonatal outcomes for patients positive for COVID-19 who were asymptomatic,

symptomatic, and those requiring oxygen support. Analyzing patient characteristics across different levels of disease severity allowed us to identify potential risk factors for worsening disease.

Our results confirm prior findings¹⁰ that 4 to 5% of all delivered COVID-19 patients present with or develop severe disease requiring oxygen support and that diagnosis occurred most commonly in the third trimester. In addition, similarly to Khoury et al, 61% of COVID-19 pregnant women are asymptomatic (compared with 62% in our cohort) and only 26% were symptomatic (compared with 38% in our cohort).⁴ Disease progression was not observed throughout our cohort.

A significant association was found between gestational age at presentation and disease severity. The median gestational age at symptom onset or diagnosis for asymptomatic patients was 37 weeks, 33 weeks for symptomatic individuals, and 36 weeks for those requiring oxygen support. This may suggest an increased risk of severe COVID-19 infection during the later stages of pregnancy. A similar pattern has been described with influenza infection.¹¹ The latter may be secondary to physiologic changes that occur during pregnancy such as the increased oxygen demand, cephalad displacement of the diaphragm, or immune system adaptations.

The later gestational age observed in asymptomatic patients was likely seen as a result of universal screening at the time of scheduled delivery. This difference may be eliminated if more widespread testing was performed for asymptomatic individuals earlier in pregnancy.

In nonpregnant adults, coexisting medical conditions have been seen more commonly in patients with severe COVID-19.¹² One study has also demonstrated this finding in infected pregnant patients.³ This was not replicated in our analysis. This may be due to the relative infrequency of comorbid medical conditions in our younger pregnant population. Other patient characteristics, including age, BMI, and race/ethnicity, did not influence disease severity. The majority of patients across all groups had an unidentified exposure. However, household exposures were identified more frequently in symptomatic individuals and those requiring oxygen support than in asymptomatic women.

Laboratory findings that were significantly associated with severity of disease included decreasing hemoglobin and white blood cell count, lymphopenia, and increasing inflammatory markers such as CRP, ferritin, and procalcitonin. These findings have been previously documented in nonpregnant adults with COVID-19.^{12,13} Lymphopenia, in particular, has been well documented in association with more severe infection.¹⁴ In **Fig. 1**, we propose an algorithm illustrating initial laboratory workup for SARS-CoV-2 positive patients.

Similar to a recent report,¹⁰ maternal outcomes, such as cesarean section and preterm delivery rates were not affected by disease severity in our cohort. While there were patients who underwent either delivery or cesarean section due to COVID-19 related concerns, the rates were not significant. These rates likely differ between institutions based on individualized clinical practice.

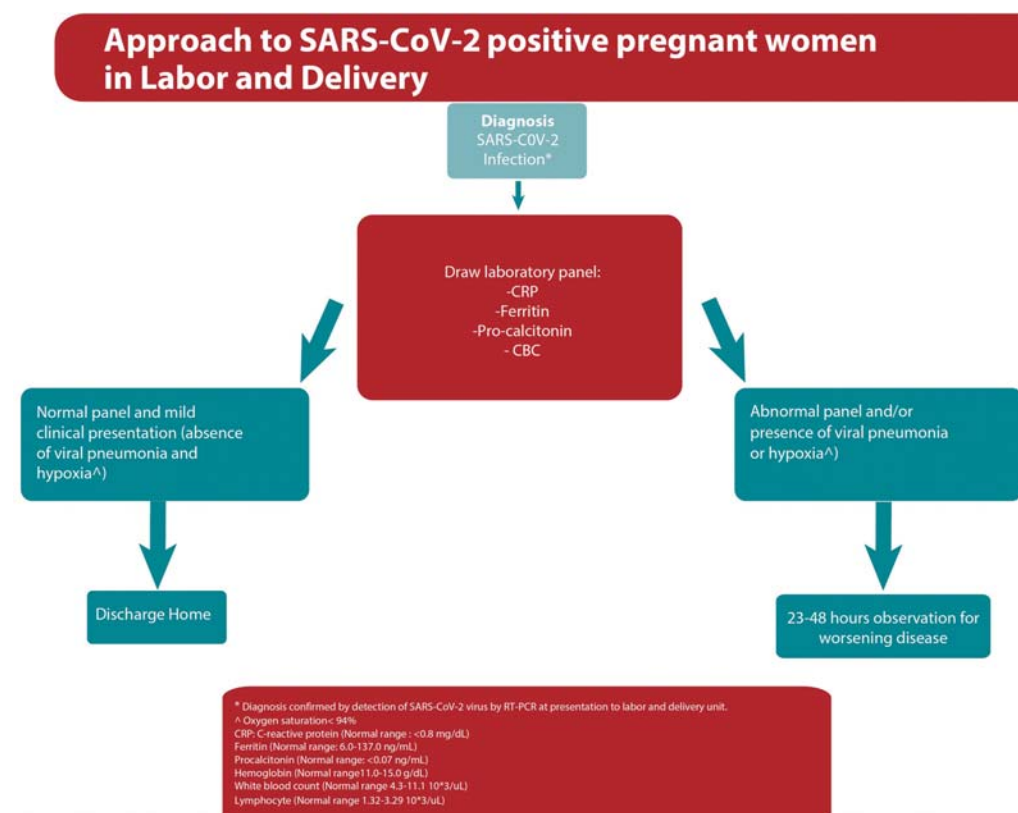


Fig. 1 Suggested initial laboratory panel for severe acute respiratory syndrome coronavirus 2 positive patients presenting to labor and delivery.

Neonatal outcomes did not differ according to maternal disease severity. Unlike prior report of neonatal positivity rates of 2%,¹⁰ in our cohort all neonates tested negative for SARS-CoV-2 24 hours after delivery. While this data are encouraging, more research is needed to fully understand that relationship between maternal SARS-CoV-2 infection and the fetus.

To summarize, the majority of pregnant patients with COVID-19 are asymptomatic, and less than 1 in 20 have disease severe enough to require oxygen support. There is insufficient evidence to accurately predict level of severity of COVID-19 in pregnant women. Women in the later stages of pregnancy may be at increased risk for severe infection and should be counseled and managed accordingly. Consideration should be given for additional risk in women with comorbid medical conditions seen associated with severe infection in nonpregnant adults. Laboratory values such as hemoglobin, white blood cell count, and inflammatory markers such as CRP, ferritin, and procalcitonin may be helpful in predicting disease severity.

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None.

Conflict of Interest

None declared.

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