Clinical course of severe and critical COVID-19 in hospitalized pregnancies: a US cohort study

Rebecca A.M. Pierce-Williams, DO[1], Julia Burd, MD [2], Laura Felder, MD [1], Rasha Khoury, MD, MPH[3], Peter S. Bernstein, MD, MPH[3], Karina Avila, MPH[4], Christina A. Penfield, MD, MPH[5], Ashley S. Roman, MD, MPH[5], Chelsea A. DeBolt, MD[6], Joanne L. Stone, MD[6], Angela Bianco, MD[6], Adina R. Kern-Goldberger, MD MPH[7], Adi Hirshberg, MD[7], Sindhu K. Srinivas, MD, MSCE[7], Jenani S. Jayakumaran, MD[8], Justin S. Brandt, MD[9], Hannah Anastasio, MD[10], Meredith Birsner, MD[10], Devon S. O'Brien, MD[11], Harish M. Sedev, MD[7], Cara D. Dolin, MD, MPH[7], William T. Schnettler, MD[12], Anju Suhag, MD[12], Shabani Ahluwalia, DO[13], Reshama S. Navathe, MD[13], Adeeb Khalifeh, MD[14], Kathryn Anderson, BA[15], Vincenzo Berghella, MD[1]

1. Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA
2. Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA
3. Division of Maternal Fetal Medicine, Department of Obstetrics & Gynecology and Women's Health, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, USA
4. Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, NY, USA
5. Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, New York University Langone Medical Center, New York, NY USA
6. Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY, USA

7. Division of Maternal-Fetal Medicine, Maternal and Child Health Research Center, Department of Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
8. Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
9. Division of Maternal Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
10. Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, St. Luke's University Health Network, Bethlehem, PA, USA
11. Department of Obstetrics & Gynecology, Saint Barnabas Medical Center, Livingston, NJ USA
12. Division of Maternal-Fetal Medicine, TriHealth-Good Samaritan Hospital, Cincinnati, OH, USA
13. Departments of Obstetrics & Gynecology, Crozer Chester Medical Center, Chester, PA, USA
14. Department of Obstetrics & Gynecology, Einstein Healthcare Network, Philadelphia, USA
15. Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

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Correspondence: Vincenzo Berghella, MD, Department of Obstetrics and Gynecology, 833 Chestnut St., Philadelphia, PA 19107 USA Tel: 215-955-5000

Email: Vincenzo.Berghella@jefferson.edu

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AJOG at a Glance:

A. Why was this study conducted?

To describe the clinical course of hospitalized pregnant patients with severe or critical COVID-19 disease so that providers have guidance regarding antepartum and delivery management.

B. What are the key findings?

Pregnant women hospitalized with severe or critical COVID-19 are admitted about 7 days after the onset of symptoms and stay 6 days (median 6 days severe and 10.5 days critical, p=0.01). If required, intubation usually occurs around day 9; peak respiratory support for severe women occurs on day 8. Hospitalization for severe or critical COVID-19 infection resulted in delivery during the course of infection in 50% of this cohort. Seventy-five percent of all women with critical COVID-19 had mostly iatrogenic preterm birth.

C. What does this study add to what is already known?

These data add significantly to the body of literature regarding the hospital course of severe or critical COVID-19 infection in pregnancy, and suggest that the clinical course of severe or critical COVID-19 infection in hospitalized pregnant women may be shorter than in non-pregnant persons.

Keywords: COVID-19, SARs-CoV2, coronavirus, pregnancy

Abstract

Background: The COVID-19 pandemic has had an impact on healthcare systems around the world with 3.0 million infected and 208,000 resultant mortalities as of this writing. Information regarding infection in pregnancy is still limited.

Objectives: To describe the clinical course of severe and critical infection in hospitalized pregnant women with positive laboratory testing for SARS-CoV2.

Study Design: This is a cohort study of pregnant women with severe or critical COVID-19 infection hospitalized at 12 US institutions between March 5, 2020 and April 20, 2020. Severe infection was defined according to published criteria by patient reported dyspnea, respiratory rate > 30 per minute, blood oxygen saturation ≤ 93% on room air, partial pressure of arterial oxygen to fraction of inspired oxygen <300 and/or lung infiltrates >50% within 24 to 48 hours on chest imaging. Critical disease was defined by respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Women were excluded if they had presumed COVID-19 infection but laboratory testing was negative. The primary outcome was median duration from hospital admission to discharge. Secondary outcomes included need for supplemental oxygen, intubation, cardiomyopathy, cardiac arrest, death, and timing of delivery. The clinical courses are described by the median disease day on which these outcomes occurred after the onset of symptoms. Treatment and neonatal outcomes are also reported.

Results: Of 64 pregnant women hospitalized with COVID-19, 44 (69%) had severe and 20 (31%) critical disease. The following pre-existing comorbidities were observed: 25% had a pulmonary condition, 17% had cardiac disease and the mean BMI was 34 kg/m^2. Gestational age at symptom onset was at a mean 29 ±6 weeks and at hospital admission a mean of 30 ±6 weeks, on a median day of disease 7 since first symptoms. Eighty-one percent of women were treated with

hydroxychloroquine; 9% of women with severe disease and 65% of women with critical disease received remdesivir. All women with critical disease received either prophylactic or therapeutic anticoagulation during their admission. The median duration of hospital stay was 6 days (6 days for severe, 10.5 days for critical, p=0.01). For those who required it, intubation usually occurred around day 9, and peak respiratory support for women with severe disease occurred on day 8. In women with critical disease, prone positioning was performed in 20% of cases, the rate of ARDS was 70%, and re-intubation was necessary in 20%. There was one case of maternal cardiac arrest, but no cases of cardiomyopathy and no maternal deaths. Thirty-two (50%) women in this cohort delivered during their COVID-19 hospitalization (34% of severe and 85% of critical women). Eighty-eight percent (15/17) of pregnant women with critical COVID-19 who delivered during their disease course were delivered preterm, 94% of them via cesarean; in all, 75% (15/20) of critically ill women delivered preterm. There were no stillbirths or neonatal deaths, or cases of vertical transmission.

Conclusion:

In hospitalized pregnant women with severe or critical COVID-19 infection, admission typically occurred about 7 days after symptom onset, and the duration of hospitalization was 6 days (6 severe versus 12 critical). Critically ill women had a high rate of ARDS, and there was one case of cardiac arrest, but there were no cases of cardiomyopathy, or maternal mortality. Hospitalization for severe or critical COVID-19 infection resulted in delivery during the course of infection in 50% of this cohort, usually in the third trimester. There were no perinatal deaths in this cohort.

Introduction

The novel Coronavirus 2019, SARS-CoV2, has caused a pandemic of COVID-19 infection, with 3.0 million infected people and 208,131 deaths globally at the time of this writing (April 27, 2020)[1]. COVID-19 infection is usually mild in 81%, severe in 14%, and critical in 5% of non-pregnant patients[2], percentages which are similar (86%, 9%, and 5%) to pregnant women in early reports[3].

The clinical course in non-pregnant patients who develop severe or critical infection include hospital admission occurring at a median of 7 days after the onset of symptoms, dyspnea on day 8, sepsis on day 9, acute respiratory distress syndrome (ARDS) on days 9-12, ICU admission and mechanical ventilation on days 10.5-12, and death or discharge for survivors on day 21; the median length of hospital stay in non-pregnant individuals is about 12 days[4–6]. However, there is very limited information regarding the clinical course of severe and critical COVID-19 infection in hospitalized pregnant women. In 1 cohort of 15 pregnant women in China, the interval from symptom onset to admission varied from 2-10 days, and no other clinical course details were provided[7].

Knowledge of the maternal course of disease is vital to answering questions about the management for pregnant women infected with COVID-19. The physiologic changes in pregnancy affect lung volumes and immune response and therefore have the potential to impact the clinical course of COVID-19 in pregnancy. To be able to answer questions about optimal management, timing of delivery and various medications used for obstetric indications, the course of maternal disease must be understood. The physiologic changes of pregnancy, particularly those related to disease severity, progression, and outcomes, also need to be more clearly elucidated.

The objective of this study was to describe the clinical course of pregnant women admitted with severe and/or critical COVID-19 infection.

Materials and Methods:

Study Design

This is a multi-center cohort study on pregnant women admitted to the hospital for treatment of severe and/or critical COVID-19 infection from March 5 to April 20, 2020. To maximize the number of cases included, this study was of both retrospective and prospective nature. It was designed in accordance with the STROBE guidelines for cohort studies prior to data collection[8]. IRB approval was obtained from the primary site, Thomas Jefferson University (IRB Control Number 20E.397). Data use agreements were obtained for collaboration between sites.

Inclusion criteria were all pregnant and immediately postpartum women confirmed SARS-CoV2 positive by laboratory testing meeting criteria for diagnosis of severe or critical COVID-19 as defined by the Chinese Center for Disease Control and Prevention[9]. Severe COVID-19 was defined as dyspnea, respiratory rate of ≥ 30 breaths per minute, blood oxygen saturation $\leq 93\%$ on room air, partial pressure of arterial oxygen to fraction of inspired oxygen <300 and/or lung infiltrates >50% within 24 to 48 hours of symptom onset[9]. For the purpose of the definition of severe disease in this study, "dyspnea" was defined as patient reported dyspnea at rest. Critical COVID-19 was defined as respiratory failure requiring mechanical ventilation, septic shock, and/or multiple organ dysfunction or failure[9]. Respiratory failure was defined as a need for invasive mechanical ventilation. Septic shock was defined as ≥2 Sepsis-related Organ Failure Assessment (SOFA) criteria [decline in partial pressure of oxygen/fraction of inspired oxygen, decline in platelets, rising bilirubin, decline in mean arterial pressure (MAP), decline in Glasgow

Coma Scale, and rise in serum creatinine] and with need for vasopressors to maintain MAP $\geq$ 65 and serum lactate >2 mmol/L even with sufficient volume resuscitation[10]. Women were considered to have multiple organ dysfunction or failure if they had evidence of at least 2 of the following: r renal impairment or failure (defined as a threefold increase in baseline creatinine or need for dialysis[11]), liver failure (INR >1.5), refractory hypoglycemia as diagnosed by the treating institution, or hepatic encephalopathy[12]. Women with inconclusive or negative COVID testing (even if clinical suspicion was high), and those diagnosed with COVID-19 diagnosis >7 days postpartum were excluded.

The primary outcome was median duration (from hospital admission to discharge) overall and for women with severe versus critical COVID-19 infection. This outcome was chosen as a surrogate for the length of illness requiring support. Secondary maternal outcomes focus on the clinical course of COVID-19, with the day of symptom onset being defined as disease day number one. The variables of the clinical course examined included disease day of oxygen supplementation, other respiratory support, intubation and extubation, day of peak respiratory support, and day of return to room air. Data were also recorded on new onset cardiomyopathy, cardiac arrest, and death. Disease day of delivery, if applicable, was included. Peak levels of various serum labs markers were recorded, as well as the peak day of that lab value if it was drawn $\geq$3 times in that patient. Additional data were collected on duration of hospitalization, treatment modalities, obstetric outcomes, and neonatal outcomes.

Data collection

Investigators at each institution reviewed their electronic medical record of the mother and any delivered neonate and de-identified data were recorded and stored in a standardized computer spreadsheet. Data were reviewed by co-investigators and compiled for analysis.

Statistical analysis

Statistical analysis included means and standard deviations for normally distributed data, medians with interquartile ranges and percentages. The groups were compared using the t-test, analysis of variance, Mann-Whitney U, χ^2 and Fisher Exact test. Analysis was performed for severe and critical illness separately, as well as for the entire cohort.

Results:

Twelve institutions, in Pennsylvania (n=6), New York (n=3), New Jersey (n=2), and Ohio (n=1), provided data. Of 64 women included, 44 (69%) had severe and 20 (31%) met criteria for critical COVID-19 infection (Figure 1).

Maternal demographics are shown in Table 1. Overall, the mean age was 33 years old; critically ill women were significantly older than severely ill women. Average body mass index (BMI) was 34 kg/m^2, and 31% women were Hispanic, 28% non-Hispanic Black, and 25% non-Hispanic white. Pre-existing pulmonary conditions (i.e. obstructive sleep apnea, asthma, chronic obstructive pulmonary disease) were present in 25% of women and pre-existing cardiac disease (i.e. chronic hypertension, cardiomyopathy) in 17% of women.

The average gestational age at symptom onset of COVID-19 infection was 29.1±7.4 weeks (range 16.6-39.1 weeks), with hospital admission at 29.9±7.3 weeks. No patients included in this study were postpartum at the onset of symptoms or hospitalization. Twenty-three percent of women with severe disease experienced symptom onset at <24 weeks, whereas all women with critical disease were >24 weeks (p=0.024). Sixty-nine percent of all women developed symptoms <34 weeks, and 86% at <37 weeks. Ninety-eight percent had disease confirmed by nasopharyngeal testing. Two critically ill women initially tested negative; one subsequently tested positive by bronchoalveolar

lavage (after 3 negative nasopharyngeal swabs over 6 days, and the other by repeat nasopharyngeal testing, Table 2. The vast majority of women in this study were treated with hydroxychloroquine (81%) (Table 3). Remdesivir was used in 25% of all women (65% of critically ill women). Convalescent serum was used in one critically ill patient. Twenty-three percent of women (55% of women with critical disease) received steroids for maternal indications (rather than for fetal maturity). All 20 (100%) of women with critical disease received either prophylactic or therapeutic anticoagulation during their admission (12/20, 60% prophylactic, 8/20, 40% therapeutic), while 27/44 (61%) of women with severe disease received anticoagulation, (25/44, 57% prophylactic, 2/44, 5% therapeutic) (Table 3).

In this cohort, 73% of women with severe disease required O_2 supplementation, while 95% (19 of 20) of the critically ill women required intubation (Table 3). In women with critical disease, 70% (14 of 20) developed ARDS, 20% (n=4) were placed in prone positioning (gestational ages 26-31 weeks), and 20% required re-intubation. At the time of writing, there were no cases of cardiomyopathy and no maternal mortality. One woman experienced cardiac arrest after a prolonged disease course. She was hospitalized 14 days after symptom onset, intubated 6 days later at 20 days from symptom onset. She remained intubated for approximately 1 week, with initial signs of recovery and extubation; however, she again developed respiratory failure and experienced cardiac arrest on day 31. Cardiopulmonary resuscitation (CPR) was performed, she was re-intubated and return of spontaneous circulation (ROSC) was achieved. She was delivered via cesarean after ROSC. She was intubated for over 2 weeks postpartum before she underwent tracheostomy placement.

In this cohort and at the time of writing, we observed that the median day (with interquartile range, IQR) of events from the first day of reported symptoms were as follows (Table 4, Figure 2):

Hospital admission on day 7 (IQR 5-9), initiation of supplemental O_2 on day 8 (IQR 5-10), intubation (among critical women) on day 9 (IQR 6-11.5), peak respiratory support on day 8.5 (IQR 6-11), hydroxychloroquine treatment started on day 8 (IQR 6-11), remdesivir treatment on day 10.5 (IQR 8.8-12.5), discontinuation of supplemental O_2 on day 13 (IQR 9-17) (2 severe and 11 critical remain on O_2 at the time of writing), symptom resolution on day 15 (IQR 11.5-20) (for those who have achieved resolution). Of those who were delivered during the disease course, delivery occurred on a median disease day 10 (IQR 6-1). When comparing severe and critical women, the clinical course was longer for the critical group, requiring the use of invasive mechanical ventilation, later cessation of supplemental oxygen (median day 12 [IQR 8-16] versus day 17 [IQR 14-22], p=0.014), last fever (median day 9 [IQR 6-10] versus 17.5 [IQR 14-20.5], p <0.00001), symptoms (median day 13.5 [IQR 10-18.5] versus 20 [IQR 15.5-22], p=0.029) and later hospital discharge (median day 12 [IQR 9.3-15.8] versus 17 [IQR 16-25], p=0.0056). The supplementary table shows for disease day of events in COVID course by gestational age cutoffs. If the laboratory studies typically utilized to predict disease severity are used as a proxy for the most severe point in the course of the infection, the average peak disease day was 11 (Table 5). Subjects with critical disease had higher interleukin-6 levels (IL-6), ferritin, fibrin split products, platelets, procalcitonin, troponins, C-reactive protein (CRP), creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) compared to those with severe disease.

The median duration of COVID-19 infection for the 51 women for whom complete hospital disease course data are available are shown in Table 6. Symptoms lasted 15 days for those whose symptoms have resolved, (n=29, 13 versus 19 days for women with severe versus critical disease, p=0.099). For the primary outcome, the length of hospital stay was on average 8±5 days (median duration 6 days). Women with severe disease were hospitalized for 6 days (IQR 4.3-7), and women

with critical disease for 12 (IQR 7-16) days (p=0.0031). At the time of writing, several women remain hospitalized (n=13, 2 severe and 11 critical). Women required supplemental O_2 for a duration of 6 days (5 [IQR 3-7] days for severe disease and 10 [IQR 7-16] for critical disease, *p*=0.0038). Of the women who were intubated and have been discharged, the median duration of intubation was 3 days (IQR 2-8).

Among all women who delivered, preterm birth <34 weeks and <37 weeks occurred in 10 (31.2 %) and 19 women (59.4%), respectively; however, when evaluating only women with critical disease who delivered (n=17), 15 (88%) were delivered preterm (Table 7). Spontaneous preterm labor occurred in only 2 women, both in the critical group (10%). During the course of COVID-19, 50% of women were delivered (34% of the women with severe disease and 85% of those with critical disease), Table 7. Maternal status was the primary indication in most cases (69% overall, 60% of severe, 76% of critical). The remainder were for fetal indications. Critical COVID women were delivered at an earlier mean gestational age than those with severe disease (32±4 weeks versus 37±2, p <0.0001). There were no cases of intrauterine fetal demise. Delivery route was cesarean for 53% and 94% of women with severe and critical disease, respectively. Preeclampsia or gestational hypertension occurred in only 2 women (3%), though 50% of our cohort remains undelivered. The rate of postpartum hemorrhage, defined as blood loss >1000 cc at time of vaginal or cesarean delivery or symptomatic hypovolemia within 24 hours associated with blood loss, was 9% overall (13% among subjects in the severe disease group, 6% of those in the critical disease group. The rate of presumed intrauterine infections (chorioamnionitis and/or endometritis) was 9% (20% among subjects in the severe disease group, 0 in the critical disease group).

The average neonatal birth weight was 2,403.3±858.0 grams (2,945.8±509.2 grams severe and 1,924.6±846.6 grams critical), though this difference is likely attributed to the earlier gestational

age of delivery in the critical disease group. Sixty-four percent of neonates required intensive care unit admission (40% of severe, 83% of critical). Additional neonatal outcomes are reported in Table 8. Detailed data on neonatal testing and/or method of testing were not available. One of 33 neonates was diagnosed with COVID-19; in this newborn, the first test for SARs-CoV2 at 24 hours of life was negative, but a repeat test at 48 hours returned a positive result. The neonate showed no signs or symptoms of COVID-19.

Discussion:

Principal findings

In this cohort, pregnant women hospitalized with severe or critical COVID-19 infection were typically admitted on day of disease 7 (as measured from the first day of symptoms), and the median duration of hospitalization was 6 days (6 versus 10.5 for severe and critical, respectively). For those who require it, intubation usually occurs around disease day 9 (approximately 2 days after hospital admission), and peak severity of non-intubated (severe) disease, judging by highest oxygen use, was approximately day 9. Fifty percent of women were delivered during their COVID-19 hospital course, the majority of these due to maternal disease. About half of the severe cases delivered vaginally, while over 90% of the critical ones delivered via cesarean. The average gestational age at delivery was 37 weeks for severe and 32 weeks for critical cases. The majority of preterm births were due to maternal status; however, data on exact etiologies were not collected. There were no maternal deaths as of this manuscript submission.

Results in the context of what is known

The clinical course of disease in hospitalized pregnant women with severe or critical COVID-19 infection seems to be similar to non-pregnant persons in the limited available studies. Notably,

these comparisons are limited as comparison patients include a broad age range, an international community, non-pregnant patients, men, and varied indications for admission. In a series of 41 non-pregnant patients in China, hospital admission occurred on disease day 7 with onset of dyspnea on day 8. ARDS occurred on day 9, and ICU admission and mechanical ventilation on day 10.5[4]. In another study of non-pregnant patients from China, the length of hospital stay was 12 days[6]. In a cohort of 191 hospitalized non-pregnant patients, ARDS and ICU admission occurred on day 12, and death on day 18.5 or discharge on day 22[5]. In a cohort of 15 pregnant women in China, the interval from symptom onset to admission was 2-10 days. Notably, this cohort does not include any patients who required invasive mechanical ventilation[7]. It is important to note that these non-pregnant populations were mostly older men, and an appropriate non-pregnant reproductive age control group is not yet available in the literature.

A current challenge lies in the prediction of patients presenting with COVID-19 infection who will progress to develop critical disease. Consistently across studies in non-pregnant populations, the risk of adverse outcomes increases with age and comorbidities, as well as certain laboratory values and radiologic findings[5, 13-16]. In one study, patients requiring ICU care were more likely to have comorbid hypertension, cardiovascular disease, diabetes, and cerebrovascular disease[16]. In terms of prognostic lab parameters, more severe lymphopenia has been noted in patients with worse outcomes[4,5,13,16-18]. Other lab markers linked with severe illness include elevated D-dimer, interleukin-6, and serum ferritin levels[5,16,18].

As there are currently few reports of severe or critical COVID-19 infections in pregnant women, this study seeks to describe these patients and their clinical progression. In previous outbreaks of respiratory pathogens, pregnant populations experienced increased severity of illness and mortality. However, current data in the COVID-19 pandemic suggests that pregnant women

experience similar, or even lower, rates of severe disease as compared to non-pregnant individuals[3,19]. Despite these early findings, there is concern that pregnant women may still be at a higher risk for complications. For example, case reports have indicated cardiomyopathy in the setting of COVID-19[20]. Further data are needed on when this occurs and what predicts its occurrence. It is therefore critical to determine the unique factors in pregnant women that predict a more severe disease course to guide clinical management as well as the optimal time of delivery.

Clinical implication and research implications

These data can help guide obstetricians in deciding when a patient should be symptomatically improving or at risk for deterioration. This is particularly important for the obstetrician who needs to consider timing and mode of delivery for patients with severe or critical COVID-19[21]. Typically, attempts should be made to support the mother with oxygen as needed to maintain an oxygen saturation >95% and reassuring fetal testing. Markers of developing critical infection seem to be valid in pregnancy as well (Table 5), but further research is needed given that the physiology of pregnancy changes the normal ranges of several of these markers, with the ultimate aim of developing a tool to predict those who would benefit from delivery. One useful variable is time: in our data, pregnant women with COVID-19 who developed critical disease and needed intubation progressed quickly from admission on day 7 from symptom onset to intubation on day 9. As the standard deviation for time to intubation is 4.5 days, this means that 95% of women requiring intubation will do so within 20 days of symptom onset; this is still a long period, when management is most difficult. As most women with severe disease do not develop critical illness, expectant supportive management is probably reasonable for most. On the other end of the spectrum, for those women at >34 weeks with several risk factors for critical disease such as advanced age, comorbidities including obesity, pulmonary or cardiac disease, diabetes and others,

predictive laboratory abnormalities, and predictive respiratory requirements, delivery may be indicated before onset of critical disease. These are challenging cases to manage, often requiring individualized decisions, particularly given that we do not know whether cesarean delivery increases the severity of the clinical course, particularly given the significant fluid shifts. A predictive tool to determine those who would benefit from delivery during COVID-19 hospitalization could be developed as we acquire more data.

Strengths and Limitations

To date, we are not aware of a larger cohort study examining specifically the disease course of pregnant women hospitalized with molecular test confirmed severe or critical COVID-19. A recent report of COVID-19 in pregnant women from Wuhan, China examined 118 pregnant women with COVID-19. Of this cohort, only 10 women had severe or critical disease, and no data were described for disease course[22].

Our study is limited by the nature of the cohort study (non-randomized, lack of control group for comparison). Additionally, management of COVID-19 varied across institutions. Due to the urgency of obtaining information on COVID-19 in pregnancy, in order to guide physician management during this pandemic, we are unable to report on long-term pregnancy or neonatal outcomes at this time.

These data are also limited by the fact that 13 women (2 severe and 11 critical) remained hospitalized, with several still on invasive mechanical ventilation, at the time of data collection; therefore, data on complete hospital courses and complete COVID-19 courses and pregnancy outcomes are limited. Fifty percent of women are undelivered, which can be seen as a strength in that in the appropriate setting, delivery can be delayed; however, complete outcomes on pregnancy cannot be reported. Specifically, effects of COVID-19 on pregnancy, including fetal growth

restriction and amniotic fluid abnormalities, could not be elucidated due to the timing of data collection. Longer term analysis will be required in the future.

Recommendations on pharmacotherapy cannot be made based on these data. Larger case-control studies of the course of COVID-19 in pregnancy, and randomized-controlled trials (RCTs) of interventions, are necessary to best determine prognosis and management of these women. Hydroxychloroquine was used in 81% of women in our study; however, current recommendations are for its use only in the setting of clinical trials due to unclear risks and benefits[23]. Based on limited data from an RCT on treatment of Ebola virus with remdesivir, the medication appears safe in pregnancy[24]. Twenty-five percent of our cohort received remdesivir. RCTs are on-going on the efficacy of Remdesivir for COVID-19 infection. At some of our institutions, RCTs on the use of convalescent plasma are ongoing, and include pregnant women. Anticoagulation remains controversial, with more research needed. By study design, no data are provided for mild COVID-19 disease.

Conclusions

Pregnant women hospitalized with severe or critical COVID-19 infection are typically admitted on day of disease 7, and stay 6 days. For those who require it, intubation usually occurs around day 9 and peak severity of non-intubated disease occurs on day 9 as well. Laboratory and treatment management can reasonably follow non-pregnant guidelines, though differing normal ranges for some laboratory values in pregnancy must be considered. This clinical course is not markedly different from that of non-pregnant hospitalized patients with COVID-19, except that days in hospital are less, with lower mortality, albeit this comparison is made with non-pregnant patients who are much older on average. This suggests that perhaps pregnancy should not be considered an independent risk factor for severe or critical COVID-19 disease. Maternal mortalities have been

rarely reported so far in the literature[25,26]; however, the sample sizes of pregnancy studies remain small and further research is necessary. Unique to pregnancy, complications such as preterm birth and need for delivery are common for women with severe or critical COVID-19 infection. This information is important in counseling women diagnosed at the early stage of disease on the potential for progression to a severe or critical stage. As management of these cases is complex, we recommend a multidisciplinary approach with Maternal-Fetal Medicine, Infectious Disease, and Critical Care Physicians. We encourage you to use these data when deciding on pregnancy management decisions and in counselling family about the progression of COVID-19 infection in the US.

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Table 1: Maternal Demographics

Characteristic	**All (n=64)**	**Severe (n=44)**	**Critical (n=20)**	**p-value**

Maternal age (years)	33.2±5.8	32.0±6.0	35.9±4.3	0.011
BMI kg/m2	33.5±7.1	33.5±7.3	29.7±5.1	0.003
Race and Ethnicity				0.21
Non-Hispanic b lack	18 (28%)	13 (30%)	5 (25%)	
Non-Hispanic white	16 (25%)	9 (20%)	7 (35%)	
Hispanic	20 (31%)	17 (39%)	3 (15%)	
Asian/Pacific Islander	3 (5%)	1 (2%)	2 (10%)	
Other	7 (11%)	4 (9%)	3 (15%)	
Singleton pregnancy	63 (98%)	44 (100%)	19 (95%)	0.135
Multiparous	46 (72%)	30 (68%)	16 (80%)	0.33
Insurance type				0.014
State	26 (41%)	21 (48%)	5 (25%)	
Private	35 (55%)	23 (52%)	12 (60%)	
Uninsured	3 (5%)	0 (0%)	3 (15%)	
Pulmonary pathology (OSA, asthma, COPD, etc.)	16 (25%)	12 (27%)	4 (20%)	0.76
Cardiac disease (including chronic hypertension, cardiomyopathy)	11 (17%)	8 (18%)	3 (15%)	1.00

Data reported as mean ± standard deviation or number (percentage)
Abbreviations: OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease

Table 2: COVID-19 infection initial findings

Characteristic	All (n=64)	Severe (n=44)	Critical (n=20)	p-value
Gestational age at onset of symptoms (weeks)	29.9±5.8	29.9±6.3	29.7±4.6	0.899
Symptom onset <24 weeks	10 (15.6%)	10 (22.7%)	0 (0%)	0.024
Symptom onset <34 weeks	44 (68.8%)	29 (69.9%)	15 (75%)	0.47
Symptom onset <37 weeks	55 (85.9%)	36 (81.8%)	19 (95%)	0.16
Gestational age at hospitalization (weeks)	30.7±5.7	30.8±6.2	30.6±4.5	0.898
Initial negative testing	2 (3%)	0 (0%)	2 (10%)	0.094
Source of positive COVID sample				
Nasopharyngeal	63 (98%)	44 (100%)	19 (95%)	0.14
Bronchoalveolar lavage (BAL)	1 (2%)	0 (0%)	1 (5%)	

Data reported as mean ± standard deviation or number (%)
** n=64 women in total; n=44 severe (symptom onset <24 weeks n=10, 24 to <34 weeks n=19, 34 to <37 weeks n=7, ≥37 weeks n=8); n=20 critical (symptom onset <24 weeks n=0, 24 to <34 weeks n=15, 34 to <37 weeks n=4, ≥37 weeks n=1)*
† 6 women remained intubated at the time of writing
‡§ 2 severe & 11 critical remained on O_2 & admitted at time of writing
/Deliveries: None delivered <24 weeks, 24 to <34 weeks n=2 severe, 12 critical; 34 to <37 weeks n=5 severe, n=4 critical; ≥ 37 weeks n=8 severe, n=1 critical

Table 3: COVID 19 Management

Characteristic	**All (n=64)**	**Severe (n=44)**	**Critical (n=20)**	**p value**
Hydroxychloroquine	52 (81%)	33 (75%)	19 (95%)	0.06
Antibiotic treatment for CAP	36 (56%)	22 (50%)	14 (70%)	0.14
Remdesivir	16 (25%)	3 (7%)	13 (65%)	<0.001
Convalescent serum	1 (2%)	0 (0%)	1 (5%)	0.31
Steroids for maternal treatment	15 (23%)	4 (9%)	11 (55%)	<0.001
Anticoagulation during admission				
Prophylactic heparin/LMWH	37 (58%)	25 (57%)	12 (60%)	0.81
Therapeutic heparin/LMWH	10 (16%)	2 (5%)	8 (40%)	<0.001
Supplemental O2	52 (81%)	32 (73%)	20 (100%)	0.01
High flow nasal cannula	16 (25%)	5 (11%)	11 (55%)	<0.0001
BiPAP/CPAP	5 (8%)	1 (2%)	4 (20%)	0.03
Intubated	19 (30%)	0 (0%)	19 (95%)	<0.001
Re-intubated	4 (6%)	0 (0%)	4 (20%)	0.008
Prone positioning	4 (6%)	0 (0%)	4 (20%)	0.008

ECMO	0 (0%)	0 (0%)	0 (0%)	1.00
ARDS	14 (22%)	0 (0%)	14 (70%)	<0.001
New onset maternal cardiomyopathy	0 (0%)	0 (0%)	0 (0%)	1.00
Maternal cardiac arrest	1 (2%)	0 (0%)	1 (5%)	<0.001
Maternal mortality	0 (0%)	0 (0%)	0 (0%)	1.00

Data reported as number (percentage)
Abbreviations: CAP, community acquired pneumonia; LMWH, low molecular weight heparin; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation, ARDS, acute respiratory distress syndrome

Table 4: Average Disease Day of events in COVID course (Day 1 = 1st day of symptoms)

Characteristic	All (n=64)	Severe (n=44)	Critical (n=20)	p-value
Inpatient admission	7 (5-9)	7 (5-9)	7 (5-10)	0.98
Hydroxychloroquine	8 (6-11)	8 (6-11)	8 (5.5-10.5)	0.77
Remdesivir	10.5 (8.8-12.5)	10 (9.5-10.5)	11 (8-14)	0.80
Antibiotics for CAP	8 (5-10)	8 (6-10)	8 (5-9)	0.43
Supplemental O_2 Started	8 (5-10)	8 (6-9)	7 (5-10)	0.54
Peak respiratory support	8.5 (6-11)	8 (7-11)	9 (6-11.5)	0.89
High flow nasal cannula	9 (7-11)	9 (7.8-10)	9 (6-11)	0.80
BiPAP/CPAP	12 (10-19)	10 (-)**	15.5 (10-20)	-
Intubation	9 (6-11.5)	-	9 (6-11.5)	-
Re-intubation	23 (20.3-25.8)	-	23 (20.3-25.8)	-
Final Extubation*	15.5 (12-18.8)	-	15.5 (12-18.8)	
Supplemental O_2 discontinued†	13 (9 -17)	12 (8-16)	17 (14-22)	0.014
Last fever	9 (7-15)	9 (6-10)	17.5 (14-20.5)	<0.00001
Hospital Discharge, (n=51)‡	12 (10-16.5)	12 (9.3-15.8)	17 (16-25)	0.0056
Symptom resolution§	15 (11.5-20)	13.5 (10-18.5)	20 (15.5-22)	0.029

Delivery (n=32)	10 (6-13)	8 (6-12)	12 (6-13)	0.35
Maternal cardiac arrest (n=1)	31	-	31	

Data reported as median (interquartile range)
Abbreviations: CAP, community acquired pneumonia; NA, not applicable; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure;
**5 women remained intubated at the time of writing; ** 1 woman only.*
† ‡2 severe & 11 critical remained on O_2 & admitted at time of writing (n=50 O_2 discontinued)
§n=29 women have achieved resolution of symptoms

Table 5: Peak Laboratory Prognostic Markers

Laboratory Values*	**All (n=64)**	**Severe (n=44)**	**Critical (n=20)**	**p-value**
IL 6 (pg/mL), [≤1.8 pg/mL†]	70.4±68.1	40.0±27.6	93.2±81.8	0.008
Ferritin (ng/mL) [5-130]	311.0±647.5	195.7±192.8	469.5±967.3	0.0003
Disease day of peak‡	13.0±6.1	11.1±4.3	15.2±7.4	0.007
Fibrin split products (mcg/mL)	690.8±405.7	843.0±181.7	462.5±647.0	0.0006
Disease day of peak	11.1±4.3	8.7±1.2	18	
Liver enzymes: [5-35]				
AST	74.0±70.2	71.4±82.2	79.3±35.6	0.68
ALT	60.2±59.8	53.0±58.4	74.8±61.5	0.18
Disease day of peak	11.4±6.1	10.0±5.0	13.9±7.3	0.015
Platelets (1,000/L) [150-420]	350.1±153.1	307.8±123.2	441.2±173.7	0.001
Disease day of peak	13.0±6.5	11.1±5.7	16.8±6.5	0.0007
D-dimer (ng/mL) [100-1500]	1,325.6±3,388.5	745.5±979.5	2,014.4±4,893.1	0.101
Disease day of peak	13.3±6.8	12.3±7.6	14.5±6.0	0.26
PT [10-13 sec]	12.9±1.4	12.3±0.9	13.8±1.6	<0.0001
PTT [24-38 sec]§	37.1±20.0	31.6±3.4	44.8±29.5	0.004
Disease day of peak	11.2±6.1	9.0±5.0	13.7±6.4	0.002
Procalcitonin (ng/mL) [0.01-0.1]	0.6±1.2	0.3±0.4	1.1±1.7	0.004
Disease day of peak	9.3±5.8	8.4±5.3	10.5±6.5	0.18
Troponin [<0.04]	0.7±3.0	0.01±0.01	1.5±4.5	0.03
Disease day of peak	12.0±7.5	10.4±4.6	13.1±9.1	0.12

CRP (mg/dL) [<20]	83.7±82.0	43.3±45.9	141.9±88.6	0.0001
Disease day of peak	10.9±4.7	9.9±4.4	12.2±5.0	0.068
CPK (IU/L) [13-101]	280.4±286.5	92.8±83.7	485.1±290.9	0.0001
Disease day of peak	13.2±7.0	14.4±5.5	12.4±8.1	0.25
LDH (IU/L) [80-450]	364.9±164.3	317.0±157.6	467.6±131.2	0.0004
Disease day of peak	11.1±6.0	9.4±5.1	14.6±6.4	0.0009

Data reported as value, (unit), [normal range in pregnancy]
Abbreviations:IL-6, interleukin 6; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; PTT, partial thromboplastin time; CRP, C-reactive protein; CPK, creatine phosphokinase; LDH, lactate dehydrogenase
**many of the normal ranges for these laboratory tests change by trimester*
† Reference range, non-pregnant
‡mean days ± standard deviation
§74% of women received prophylactic or therapeutic anticoagulation, which will alter coagulation study results

Table 6: Duration of COVID-19 hospital characteristics, Discharged Women

Characteristic	**All**	**Severe**	**Critical**	**p-value**
Symptoms*	15 (11-19)	13 (10-19)	19 (14-22)	0.099
Hospital stay	6 (5-8)	6 (4.3-7)	12 (7-18)	0.0031
Supplemental O_2	6 (3-8)	5 (3-7)	10 (7-16)	0.0038
Intubation	3 (2-8)	NA	3 (2-8)	

Data reported as median (interquartile range)
**Only for women who became asymptomatic (n=29)*

Table 7: Pregnancy Outcomes

Characteristic	All (n=64)	Severe (n=44)	Critical (n=20)	p-value
Steroids for fetal maturity	16 (25%)	7 (16%)	9 (45%)	0.013
Magnesium sulfate for neuroprotection	6 (9%)	0 (0%)	6 (30%)	0.001
Hypertensive disorders of pregnancy	2 (3%)	2 (5%)	0 (0%)	1.00
Magnesium sulfate for preeclampsia	1 (2%)	1 (2%)	0 (0%)	1.00
IUGR	2 (3%)	0 (0%)	2 (10%)	0.094
Stillbirth	0 (0%)	0 (0%)	0 (0%)	1.00
Oligohydramnios	1 (2%)	1 (2%)	0 (0%)	1.00
Delivered during COVID-19 infection (any cause)	32 (50%)	15 (34%)	17 (85%)	<0.001
Delivered for maternal status	22 (69%)	9 (60%)	13 (76%)	0.32
Delivered for fetal status	3 (9%)	0 (0%)	3 (18%)	0.00
Delivered for obstetric indications	7 (22%)	6 (40%)	1 (6%)	0.33
Presumed Chorioamnionitis and/or endometritis (n=32; 15 severe, 17 critical)	3 (9%)	3 (20%)	0 (0%)	0.55
Postpartum hemorrhage* (n=32; 15 severe, 17 critical)	3 (9%)	2 (13%)	1 (6%)	1.00
Preterm birth <37 weeks (n=32; 15 severe, 17 critical)	19 (29.7%)	4 (9%)	15 (75%)	<0.0001
Preterm birth < 34 weeks (n=32; 15 severe, 17 critical)	10 (15.6%)	0 (0%)	10 (50%)	<0.0001

Spontaneous preterm Labor	2 (3%)	0 (0%)	2 (10%)	0.09
PPROM	1 (2%)	1 (2%)	0 (0%)	1.00
Delivery route (n=32; 15 severe, 17 critical)				
Vaginal (includes operative vaginal delivery)	8 (25%)	7 (47%)	1 (6%)	0.009
Cesarean delivery	24 (75%)	8 (53%)	16 (94%)	

Data reported as mean ± standard deviation or number (percentage)
[*]Postpartum hemorrhage: EBL ≥1000mL or symptomatic/vital sign changes
Abbreviations: PPROM, preterm premature rupture of membranes; IUGR, intrauterine growth restriction; IUFD, intrauterine fetal demise

Table 8: Neonatal outcomes

Characteristic	**All (n=33*)**	**Severe (n=15)**	**Critical (n=18)**	**p-value**
Gestational age at delivery, weeks†	34.5±4.2	37.7±1.6	31.9±3.8	<0.001
Birth weight (grams)*	2403.3±858.0	2945.8±509.2	1924.6±846.6	<0.001
NICU Admission, n (%)	21 (63.6%)	6 (40%)	15 (83.3%)	<0.001
5-minute Apgar scores†	7.9±1.7	8.8±0.8	7.2±2.0	0.067
Neonatal death, n (%)	0 (0%)	0 (0%)	0 (0%)	1.00

Data reported as mean ± standard deviation or number (percent)
Abbreviation: NICU, neonatal intensive care unit
**1 twin pregnancy in critical group; †Mean ± Std Dev, n=15 severe, n=18 critical neonates*

Figure 1: Flow diagram of included women

Flow chart of women included who experienced a severe or critical COVID-19 infection in pregnancy.

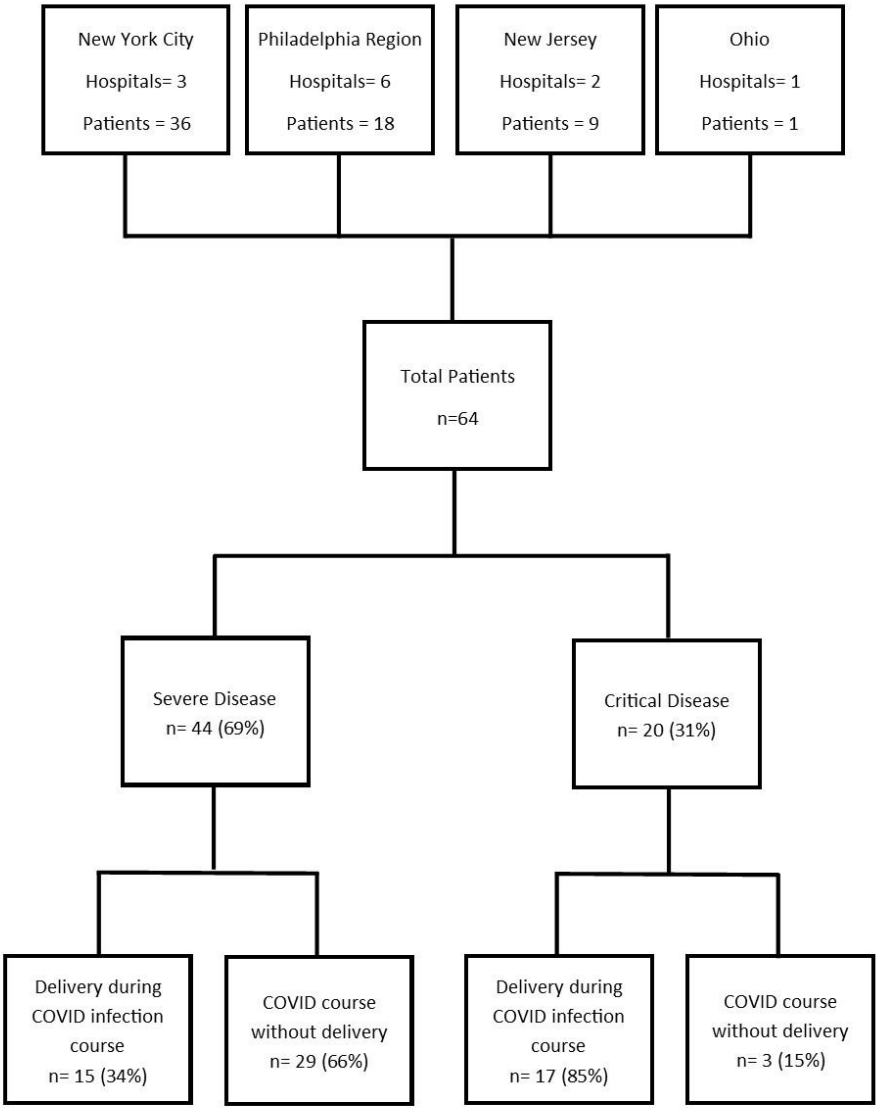
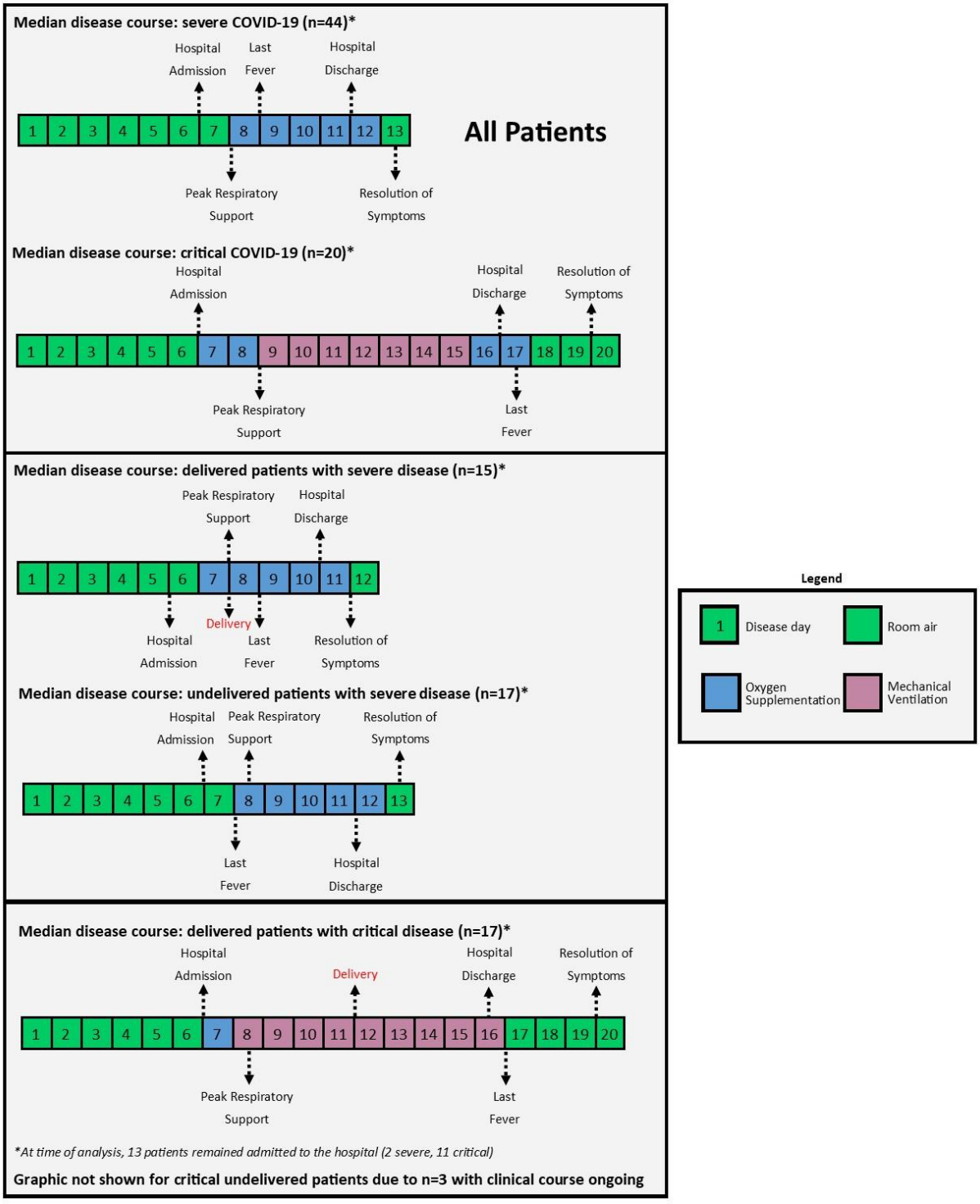


Figure 2: Median clinical course


Median disease course: severe COVID-19 (n=44)*
Hospital Admission
Last Fever
Hospital Discharge
1 2 3 4 5 6 7 8 9 10 11 12 13
All Patients
Peak Respiratory Support
Resolution of Symptoms
Median disease course: critical COVID-19 (n=20)*
Hospital Admission
Hospital Discharge
Resolution of Symptoms
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Peak Respiratory Support
Last Fever
Median disease course: delivered patients with severe disease (n=15)*
Peak Respiratory Support
Hospital Discharge
1 2 3 4 5 6 7 8 9 10 11 12
Hospital Admission
Delivery
Last Fever
Resolution of Symptoms
Median disease course: undelivered patients with severe disease (n=17)*
Hospital Admission
Peak Respiratory Support
Resolution of Symptoms
1 2 3 4 5 6 7 8 9 10 11 12 13
Last Fever
Hospital Discharge
Median disease course: delivered patients with critical disease (n=17)*
Hospital Admission
Delivery
Hospital Discharge
Resolution of Symptoms
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Peak Respiratory Support
Last Fever
*At time of analysis, 13 patients remained admitted to the hospital (2 severe, 11 critical)
Graphic not shown for critical undelivered patients due to n=3 with clinical course ongoing
Legend
1 Disease day
Room air
Oxygen Supplementation
Mechanical Ventilation

Median course of disease, separated by all patients (severe and critical) and delivered and undelivered patients (severe and critical). Notably, due to publication prior to completion of illness course in some patients, dates of oxygen discontinuation, hospital discharge, and symptom resolution may appear falsely low.

Supplementary Table:

Average Disease Day of events in COVID course (Day 1 = 1st day of symptoms), by gestational age

Characteristic	**All*** **(n=64)**	**Severe** **(n=44)**	**Critical** **(n=20)**	**p-value**

Inpatient admission				
All gestations	7 (5-9)	7 (5-9)	7 (5-10)	0.98
<24 weeks	7 (5.5-8.5)	7 (5.5-8.5)	NA	NA
24 to <34 weeks	7.5 (5-9)	8 (5.5-9)	7 (5-10)	0.76
34 to <37 weeks	8 (8-11)	8 (8-11.5)	6.5 (4.3-9)	0.26
≥37 weeks	3 (1-5)	4 (1-5.3)	1	0.89
Hydroxychloroquine				
All gestations	8 (6-11)	8 (6-11)	8 (5.5-10.5)	0.77
<24 weeks	8 (7.5-12)	8 (7.5-12)	NA	NA
24 to <34 weeks	7.5 (6-10.8)	7 (5.8-9.5)	8.5 (6-10.8)	0.35
34 to <37 weeks	8 (6.5-9)	8.5 (8-9)	6.5 (4.3-9)	0.31
≥37 weeks	7 (2.8-11.3)	11 (7-11.5)	2	0.5
Remdesivir				
All gestations	10.5 (8.8-12.5)	10 (9.5-10.5)	11 (8-14)	0.8
<24 weeks	10	10	NA	NA
24 to <34 weeks	10 (8-12)	9	10.5 (8-12.8)	0.92
34 to <37 weeks	12.5 (11.8-13.3)	11	14	1.0
≥37 weeks	NA	NA	NA	NA
Antibiotics for CAP				
All gestations	8 (5-10)	8 (6-10)	8 (5-9)	0.43
<24 weeks	8.5 (7.3-16.5)	8.5 (7.3-16.5)	NA	NA
24 to <34 weeks	8 (6-10)	8.5 (6-10.3)	8 (5.5-10)	0.94
34 to <37 weeks	8 (5.5-8)	8 (7.5-8.3)	5 (3.5-6.5)	0.23
≥37 weeks	2.5 (1.8-5)	3 (2-7)	2	1.0
Supplemental O_2 Started				
All gestations	8 (5-10)	8 (6-9)	7 (5-10)	0.54
<24 weeks	7 (4.8-7.3)	7 (4.8-7.3)	NA	NA
24 to <34 weeks	8 (6-10)	8 (6.5-10.5)	7 (5.5-10)	0.62
34 to <37 weeks	8 (7-10.5)	9 (8-12)	6.5 (4.3-9)	0.21
≥37 weeks	3.5 (1.8-5.5)	5 (3.5-6)	1	0.5
Peak respiratory support				
All gestations	8.5 (6-11)	8 (7-11)	9 (6-11.5)	0.89
<24 weeks	7 (6-7.5)	7 (6-7.5)	NA	NA
24 to <34 weeks	9 (6.3-11)	9 (7.5-11)	9 (6-11.5)	0.82
34 to <37 weeks	8.5 (6.5-14.3)	9 (8-15)	5 (3.5-8.5)	0.18
≥37 weeks	7 (2-9)	4.5 (2-8.3)	9	0.8
High flow nasal cannula				
All gestations	9 (7-11)	9 (7.8-10)	9 (6-11)	0.80
<24 weeks	7 (5.5-7.5)	7 (5.5-7.5)	NA	NA
24 to <34 weeks	9.5 (6.5-20.8)	9.5 (9-10)	9 (5.3-11)	0.98
34 to <37 weeks	14 (11-14.5)	15	11 (9.5-12.5)	0.67

≥37 weeks	9	NA	9	-
BiPAP/CPAP				
All gestations	12 (10-19)	10	15.5 (10-20)	0.8
<24 weeks	NA	NA	NA	NA
24 to <34 week	12 (10-19)	10	15.5 (10-20)	0.8
34 to <37 weeks	NA	NA	15.5 (10-20)	NA
≥37 weeks	NA	NA	15.5 (10-20)	NA
Intubation (n=18)				
All gestations	9 (6-11.5)	NA	9 (6-11.5)	-
<24 weeks	NA	NA	NA	-
24 to <34 weeks	9 (6-11.5)	NA	9 (6-11.5)	-
34 to <37 weeks	7.5 (4.3-10.5)	NA	7.5 (4.3-10.5)	-
≥37 weeks	NA	NA	NA	-
Re-intubation (n=4)				
All gestations	23 (20.3-25.8)	NA	23 (20.3-25.8)	-
<24 weeks	NA	NA	NA	-
24 to <34 weeks	23 (20.3-25.8)	NA	23 (20.3-25.8)	-
34 to <37 weeks	NA	NA	NA	-
≥37 weeks	NA	NA	NA	-
Final Extubation (n=14)†				
All gestations	15.5 (12-18.8)	NA	15.5 (12-18.8)	-
<24 weeks	NA	NA	NA	-
24 to <34 weeks	18 (13.3-19)	NA	18 (13.3-19)	-
34 to <37 weeks	9.5 (5.5-13.3)	NA	9.5 (5.5-13.3)	-
≥37 weeks	NA	NA	NA	-
O_2 discontinued‡				
All gestations	13 (8.3-17)	12 (8-16)	17 (14-22)	0.014
<24 weeks	11 (8-16.5)	11 (8-16.5)	NA	NA
24 to <34 weeks	13 (11.3-19.8)	12.5 (10.3-14.5)	21 (17.8-	0.0066
34 to <37 weeks	14 (11-17)	15 (11.5-17)	22.8)	-
≥37 weeks	5 (2.8-9.3)	5 (2.8-9.3)	14 (10.5-15)	-
			NA	
Last fever				
All gestations	9 (7-15)	9 (6-10)	17.5 (14-20.5)	<0.00001
<24 weeks	9 (7.5-10)	9 (7.5-10)	NA	NA
24 to <34 weeks	10 (6.5-17)	7.5 (6-9.8)	18 (17-21)	0.00014
34 to <37 weeks	10.5 (9-13.5)	9 (9-13.5)	13	0.57
≥37 weeks	7 (4.5-9.5)	7 (4.5-9.5)	NA	-
Hospital Discharge§				
All gestations	12 (10-16.5)	12 (9.3-15.8)	17 (16 -25	0.0056

<24 weeks **24 to <34 weeks** **34 to <37 weeks** **≥37 weeks**	11.5 (8.3-18.5) 13 (10.5 - 18.5) 15 (12-19) 7.5 (4.8-10.8)	11.5 (8.3-18.5) 12 (10-15) 14 (12-20.5) 7.5 (4.8-10.8)	) NA 23.5 (18.3 - 26.5) 16 (11.5-16) NA	NA 0.007 - -
Symptom resolution **All gestations** **<24 weeks** **24 to <34 weeks** **34 to <37 weeks** **≥37 weeks**	 15 (11.5-20) 13 (10.5-18.5) 16.5 (12.3-20) 12 (15-8.5) 16 (14-21)	 13.5 (10-18.5) 13.5 (10-18.5) 14.5 (11.5-17.3) 9 (8-12) 16 (14-21)	 20 (15.5-22) NA 20.5 (20-24) 15 (14.5-15.5) NA	 0.029 NA 0.028 0.38 -
Delivery‖ **All gestations** **<24 weeks** **24 to <34 weeks** **34 to <37 weeks** **≥37 weeks**	 10 (6-13) NA 12 (9.5-14.5) 9 (7-12) 6 (2-10)	 8 (6-12) NA 9 (7.5-10.5) 9 (8-17) 6.5 (4.3-10.5)	 12 (6-13) NA 12.5 (10.5-5.3) 7.5 (4.3-10.5) 1	 0.35 NA 0.42 0.41 0.22
Maternal cardiac arrest **All gestations** **<24 weeks** **24 to <34 weeks** **34 to <37 weeks** **≥37 weeks**	 31 NA 31 NA NA	 NA NA NA NA NA	 31 NA 31 NA NA	 - - - - -

Data reported as median (interquartile range) from symptom onset (Day 1)

Abbreviations: CAP, community acquired pneumonia; NA, not applicable; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure;
** n=64 women in total; n=44 severe (symptom onset <24 weeks n=10, 24 to <34 weeks n=19, 34 to <37 weeks n=7, ≥37 weeks n=8); n=20 critical (symptom onset <24 weeks n=0, 24 to <34 weeks n=15, 34 to <37 weeks n=4, ≥37 weeks n=1)*
† 6 women remained intubated at the time of writing
‡§ 2 severe & 11 critical remained on O_2 & admitted at time of writing
‖Deliveries: None delivered <24 weeks, 24 to <34 weeks n=2 severe, 12 critical; 34 to <37 weeks n=5 severe, n=4 critical; ≥ 37 weeks n=8 severe, n=1 critical.