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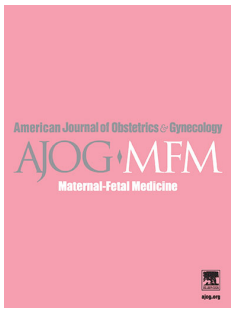

Coronavirus Disease 2019 (COVID-19) pregnancy outcomes in a racially and ethnically diverse population

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Coronavirus Disease 2019 (COVID-19) pregnancy outcomes in a racially and ethnically diverse population

Olga GRECHUKHINA, MD; Victoria GREENBERG, MD; Lisbet S. LUNDSBERG, PhD; Uma DESHMUKH, MD; Jennifer CATE, MD; Heather S. LIPKIND, MD, MS; Katherine H. CAMPBELL, MD, MPH; Christian M. PETTKER, MD; Katherine S. KOHARI, MD; Uma M. REDDY, MD, MPH.

Yale University, Department of Obstetrics, Gynecology & Reproductive Sciences, New Haven, CT

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Corresponding author: Olga Grechukhina, MD

Department of Obstetrics, Gynecology & Reproductive Sciences,

Yale School of Medicine

333 Cedar Street, New Haven, CT 06520-8063, PO Box 208063

Cell phone: 203-499-8193

Olga.grechukhina@yale.edu

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Coronavirus Disease 2019 (COVID-19) pregnancy outcomes in a racially and ethnically diverse population

Condensation: Obesity and Hispanic ethnicity are risk factors for increased COVID-19 disease severity in pregnancy.

Short Title: A series of 141 cases of COVID-19 in pregnancy

AJOG at a Glance:

A. Why was the study conducted?

- There are limited data on coronavirus disease 2019 outcomes when contracted during pregnancy.
- In this study we describe 141 cases of SARS-CoV-2 infection in pregnancy and postpartum period in a racially and ethnically diverse population.
- We sought to describe demographics of COVID-19 pregnant population, identify risk factors for worse clinical course, review laboratory trends and provide perinatal outcomes.

B. What are the key findings?

- The overall rate of moderate and severe disease was low in pregnant women in our series (4.3%); however, there was one maternal death.
- Hispanic women were disproportionately affected by SARS-CoV-2 compared to other racial/ethnic groups.
- Hispanic ethnicity and obesity were risk factors for worse clinical course.

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

- Our study identifies Hispanic ethnicity and obesity as risk factors for worse clinical course of COVID-19 in pregnancy.

ABSTRACT

Background: Older age and medical comorbidities are identified risk factors for developing severe COVID-19. However, there are limited data on risk stratification, clinical and laboratory course, and optimal management of COVID-19 in pregnancy.

Objective: Our study aims to describe the clinical course of COVID-19, effect of comorbidities on disease severity, laboratory trends, and pregnancy outcomes of symptomatic and asymptomatic SARS-CoV-2 positive pregnant women.

Study Design: This is a case series of pregnant and postpartum women who tested positive for SARS-CoV-2 between 3/1/2020 and 5/11/2020 within 3 hospitals of the Yale-New Haven Health delivery network. Charts were reviewed for basic sociodemographic and pre-pregnancy characteristics, COVID-19 course, laboratory values, and pregnancy outcomes.

Results: Out of 1,567 tested pregnant and postpartum women between 3/1/2020 and 5/11/2020, 9% (n=141) had a positive SARS-CoV-2 result. Hispanic women were overrepresented in the SARS-CoV-2 positive group (n=61; 43.8%). Additionally, Hispanic ethnicity was associated with higher rate of moderate and severe disease compared to non-Hispanic (18% (11/61) vs 3.8% (3/78), respectively, OR 5.5 95% CI 1.46-20.7, p=0.01). Forty-four women (31.2%) were asymptomatic, 37 (26.2%) of whom were diagnosed on universal screening upon admission for delivery. Fifty-nine percent (n=83) were diagnosed antepartum, 36% (n=51) upon presentation for childbirth and 5% (n=7) postpartum. Severe disease was diagnosed in 6 cases (4.3%) and there was one maternal death. Obese women were more likely to develop moderate and severe disease than non-obese women (16.4% (9/55) vs 3.8% (3/79), OR 4.96, 95%CI 1.28-19.25, p=0.02). Hypertensive disorders of pregnancy were diagnosed in 22.3% (17/77) of women who delivered after 20 weeks. Higher levels of C-reactive protein during antepartum COVID-19-related admission were more common in women with worse clinical course; this association, however, did not reach statistical significance.

Conclusion: COVID-19 in pregnancy may result in severe disease and death. Hispanic women were more likely to test positive for SARS-CoV-2 than other ethnic groups. Obesity and Hispanic ethnicity represent risk factors for moderate and severe disease.

Keywords: coronavirus, COVID-19, SARS-CoV-2, pregnancy, Hispanic ethnicity

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus, causes coronavirus disease 2019 (COVID-19) and is responsible for a global health emergency. This pandemic has led to over 29 million people infected and over 925,000 deaths worldwide (as of September 14, 2020).[1] This health crisis has spared no demographic, causing concern about its impact on vulnerable populations, such as pregnant women. [2,3]

Since the start of the pandemic, clinicians and researchers have steadily expanded the understanding of COVID-19 in pregnancy. However, the total number of cases reported in the literature remains limited. This study aims to describe the clinical course of pregnant women and their neonates in a large, diverse hospital system in a significantly affected region adjacent to New York City, one of the United States' initial infectious epicenters. Medical comorbidities and sociodemographic factors were examined for association with COVID-19 severity and clinical course. Lastly, we report laboratory trends for SARS-CoV-2 positive pregnant women admitted to the hospital.

MATERIALS AND METHODS

Study population

This is a case series of all pregnant and postpartum women with positive SARS-CoV-2 RT-PCR tests between 3/1/2020 and 5/11/2020 from three Yale New Haven Health hospitals (Yale New Haven, Bridgeport, and Greenwich hospitals). Subjects were identified using an electronic health record (EHR) search for an open pregnancy episode and a SARS-CoV-2 RT-PCR laboratory result within the timeframe. Ambulatory and inpatient testing was included. Each chart was individually reviewed for current pregnant status (positive pregnancy test with or without ultrasound confirmation) or pregnancy resolution within 6 weeks of SARS-CoV-2 test

for inclusion into the study cohort. Subjects with a positive test were included for analysis. Each case was individually reviewed to collect the following: baseline sociodemographic factors; past medical, surgical and obstetric history; antenatal course; and COVID-19 course including symptoms, laboratory and imaging studies, management, maternal, and neonatal outcomes. The study was approved by Yale University institutional review board with waiver of consent (HIC2000027797).

Testing and diagnosis of COVID-19

SARS-CoV-2 testing used RT-PCR analysis of nasopharyngeal swab specimens. Testing criteria generally consisted of either 1) patients with symptoms of COVID-19 as deemed by their healthcare provider or the institutional COVID-19 Call Center, or 2) universal testing of all pregnant women who were admitted after April 1, 2020 for delivery or antepartum management. Testing criteria of symptomatic patients evolved during the study period and were set by institutional committees guided by Centers for Disease Control and Prevention (CDC) recommendations. Neonatal testing was indicated for all newborns born to mothers who tested positive for SARS-CoV-2 within 2 weeks of the delivery and was performed by RT-PCR of nasopharyngeal samples between 24 and 48 hours of birth.[4]

Disease severity was classified per World Health Organization (WHO) into asymptomatic (no current or previous symptoms), mild (symptomatic patients without evidence of viral pneumonia or hypoxia), moderate (clinical signs of pneumonia without signs of severe pneumonia and no need for supplemental oxygen), severe (signs of severe pneumonia i.e. respiratory rate of 30/min or more, blood oxygen saturation of less than 95% [the threshold for oxygen supplementation in pregnancy], severe respiratory distress), and critical (acute respiratory distress syndrome, sepsis or septic shock).[5] Outpatient triage of the pregnant COVID-

19 population was performed per institutional guidelines (Supplemental Figure 1). For analysis, severe and critical disease were combined, resulting in a total of 4 groups. Final disease severity was assigned retrospectively according to the above definitions which were set up *a priori* by a panel of Maternal-Fetal Medicine subspecialists based on the entire course of the disease.

Race and ethnicity information were self-reported at the time of hospital registration and abstracted directly from the EHR. Hypertensive disorders of pregnancy (HDP), including gestational hypertension, preeclampsia without and with severe features, eclampsia and HELLP, were identified during individual chart review. All diagnoses were confirmed to meet the American College of Obstetricians and Gynecologists (ACOG) criteria of HDP.[6] Laboratory testing guidelines for admitted patients varied between the hospitals and evolved over time. D-dimer and C-reactive protein (CRP) were chosen for analysis as the most consistently tested and trended lab studies. Since the occurrence of birth affects the levels of these lab values, we divided our cohort into two groups for the purpose of analysis: women admitted for delivery (symptomatic and asymptomatic) and women admitted in the antepartum period and discharged undelivered.

Statistical analysis

Patient characteristics including sociodemographics, pregnancy outcomes, comorbidities, and disease severity are reported descriptively and presented as percentages of the total cohort. Continuous variables were not normally distributed and thus reported as median and interquartile range (IQR). Bivariate analysis to evaluate the association between patient characteristics, comorbidities, and disease severity was performed using Fisher exact test. Due to the low number of subjects in the moderate and severe groups, to further examine the association between ethnicity (Hispanic and non-Hispanic) and obesity (pre-pregnancy BMI ≥30 and <30

kg/m^2) with severity of the disease, the cohort was organized into two groups: asymptomatic/mild disease and moderate/severe disease. Unadjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated for these dichotomous measures. Adjusted OR were unable to be calculated due to small sample size. Tests of association between specific symptoms and disease severity were restricted to those with symptoms (n=97). In this group we evaluated the association between COVID-19 severity as a 3-level categorical measure (mild, moderate, severe) and dichotomous measures of symptoms using the Fisher exact test. Non-parametric Mann-Whitney U test was used to compare non-normally distributed continuous variables (CRP values). P value <0.05 was considered significant.

RESULTS

During the study period, 1,567 pregnant and postpartum women were evaluated for SARS-CoV-2 based on symptoms or as part of the universal testing protocol upon presentation for delivery or antepartum admission; 8.9% (141/1,567) tested positive. Fifty-nine percent (84/141) of positive patients received their care at Yale New Haven Hospital, 24.1% (34/141) at Bridgeport Hospital and 16.3% (23/141) at Greenwich Hospital. The median age of the cohort was 30 years (IQR 25-34) (Table 1). The median pre-pregnancy body mass index (BMI) was 28.4 kg/m^2 (IQR 24.1-35.1). Forty-four percent (61/141) of women were Hispanic, 27.3% (38/141) were non-Hispanic white, 21.6% (30/141) were non-Hispanic black, and 7.2% (10/141) were of Asian or other race. Among all tested women the racial/ethnic breakdown was as follows: Hispanic 23.5% (356/1,567); non-Hispanic white 54.2% (823/1,567); non-Hispanic black 13.8% (209/1,567); Asian and other 8.6% (130/1,567); data were missing on 49 tested women (data not shown). Comparison of race/ethnicity breakdown between SARS-CoV-2

positive and negative groups revealed overrepresentation of Hispanic women in the positive cohort, p<0.001. For reference, the racial/ethnic distribution of all women across three hospitals admitted for delivery during the study frame was as follows: 23.1% (480/2082) Hispanic; 56.3% (1172/2082) non-Hispanic white, 12.7% (265/2082) non-Hispanic black, 7.9% (165/2082) Asian and other. When evaluated as a dichotomous measure, Hispanic ethnicity was associated with increased odds of moderate/severe COVID-19 course compared to non-Hispanic ethnicity (18% (11/61) vs 3.8% (3/78), unadjusted OR 5.5 95% CI 1.46-20.71, p=0.01).

The median gestational age at diagnosis was 35 weeks for antepartum diagnoses (IQR 22-38.5), 39 weeks (IQR 38-39) for asymptomatic women, and 27.5 (IQR 17-36), 35 (IQR 30-36), and 26 (IQR 22-31) weeks for patients with mild, moderate and severe/critical disease, respectively. Additional demographic information and patient characteristics are described in Table 1. The diagnosis was made antenatally in 58.8% of cases (83/141): 7.8% (11/141) in the 1st trimester, 26.2% (37/141) in the 2nd trimester, and 24.8% (35/141) in the 3rd trimester. Thirty-six percent of women (51/141) were diagnosed upon admission for childbirth. Five percent (7/141) were diagnosed with COVID-19 postpartum after discharge from their childbirth admission. Thirty-one percent of women (44/141) were asymptomatic. Fifty-eight percent of women (82/141) had mild disease; 6.4% (9/141) had moderate disease. Five women had severe or critical disease. One woman died in the Emergency Room. This woman, with a pre-pregnancy BMI of 35 kg/m^2, was diagnosed with COVID-19 in ambulatory care in the first trimester of pregnancy. She developed respiratory distress at home 13 days after initial symptom onset and arrived at the Emergency Department profoundly hypoxemic, suffering cardiac arrest and ultimately died despite prolonged attempts at cardiopulmonary resuscitation. No autopsy was

168 performed. Including this case, the rate of severe/critical disease in our population was 4.3%
169 (6/141). Timing of the diagnoses and disease severity are reflected in Figure 1.

170 Maternal medical comorbidities and their relation to COVID-19 course are presented in
171 Table 1. Severity of disease was associated with obesity, both as a dichotomous measure and by
172 obesity class ($p=0.01$ and $p<0.01$, respectively) but not with any other co-morbidity. Obese
173 women had higher rates of moderate/severe disease than non-obese women (16.4% (9/55) vs
174 3.8% (3/79), unadjusted OR 4.96, 95% CI 1.28-19.25). The distribution of obesity among racial-
175 ethnic groups was as follows: Hispanic – 38.6% (22/57); non-Hispanic white - 23.7% (9/38);
176 non-Hispanic black – 73.3% (22/30); and Asian or other – 25% (2/8), $p<0.001$, suggesting that
177 Hispanic ethnicity is unlikely to be solely related to the effect of obesity on clinical course of
178 COVID-19. Obese Hispanic women were also more likely to develop moderate and severe
179 COVID-19 compared to non-obese Hispanic women (31.8% (7/22) vs 8.6% (3/35), OR 4.98,
180 95% CI 1.13-21.98).

181 Among symptomatic women, the most common symptoms in our cohort were cough
182 (70.1%), muscle aches (51.6%) and sore throat (47.4%) (Figure 2). The most common symptoms
183 in women with severe disease were muscle aches, fever, shortness of breath, nausea, chest pain
184 and abdominal pain.

185 D-dimer and CRP trends, grouped by the type of admission, are presented in Figure 3.
186 Notably, D-dimer values varied greatly within the group who tested positive for SARS-CoV-2
187 during childbirth admission. However, most had a substantial increase in D-dimer value shortly
188 after birth with a subsequent decline within 48 hours. D-dimer took longer to normalize in one
189 patient (5 days after delivery) whose respiratory status deteriorated in labor necessitating
190 cesarean birth followed by ICU admission for COVID-19-related respiratory failure. There were

no cases of venous thromboembolism diagnosed during the study period. CRP also peaked after delivery. Women admitted antepartum for COVID-19 management who developed severe disease appeared to have higher initial CRP values than those with milder disease. Comparison between these two groups, however, did not reach statistical significance (p=0.057).

Pregnancy outcomes were available for 56.7% of women (80/141) (Figure 1 and Table 2). Notably, one woman underwent termination via dilation and evacuation at 22 weeks of gestation due to severe preterm preeclampsia syndrome in the setting of COVID-19 infection.[7] Ninety-five percent of pregnancies (76/80) resulted in a live birth, 3 of which were preterm (2 - spontaneous, 1 – indicated by preeclampsia with severe features). Vaginal delivery occurred in 67.5% (52/77) of cases, and cesarean in 31.1% of cases (24/77). One cesarean birth was indicated for maternal and fetal decompensation secondary to COVID-19.

HDP affected 22.1% (17/77) of COVID-19 positive pregnancies. The rate of preeclampsia/eclampsia/HELLP was 16.9% (13/77). Twelve percent of COVID-19 positive women (2/17) had pre-existing hypertension. For comparison, the overall rates of HDP, preeclampsia/eclampsia/HELLP and pre-existing hypertension at Yale-New Haven Hospital in 2018-2019 among singleton pregnancies were 18.5% (1601/8,691), 7.6% (668/8,691) and 8.9% (770/8,691), respectively.

Nasopharyngeal swab SARS-CoV-2 RT-PCR results for all tested newborns (n=60) were negative. Placental tissue from the 22-week termination for severe preterm preeclampsia syndrome tested positive for SARS-CoV-2 RNA.[7] None of the newborns required COVID-19 related ICU admission.

COMMENT

Principal Findings

This is a series of 141 cases of COVID-19 in pregnant and postpartum women within a diverse population of Southern Connecticut. Although the rate of severe disease in our population is low (4.3%), our cohort includes one maternal death. In our cohort, Hispanic women were disproportionately affected by COVID-19 and appeared to have an increased risk of moderate/severe disease. This finding is unlikely to be related to a disproportionate testing in Hispanic population as all three hospital sites implemented universal SARS-CoV-2 testing upon admission for childbirth. Pre-pregnancy obesity was associated with a higher disease severity category. HDP affected approximately 1 out of every 5 women with COVID-19 after 20 weeks of gestation with the majority diagnosed with preeclampsia with severe features or HELLP syndrome. Our study demonstrates that delivery is associated with transient increases in D-dimer and CRP levels in all COVID-19 positive women regardless of symptomatic status. D-dimer returned to predelivery values within 24-48 hours in most women. D-dimer did not appear to be a useful marker to distinguish COVID-19 disease severity category. All newborns born to COVID-19 positive women tested negative for SARS-CoV-2 RNA via nasopharyngeal swab after 24 hours of life; however, there was one case with positive placental SARS-CoV-2 testing.[7]

Results in the Context of What is Known

Early reports of SARS-CoV-2 infection during pregnancy are encouraging as they failed to demonstrate higher susceptibility or morbidity in pregnant women compared to the general population.[8-11] More recent reports have described severe and critical disease in pregnancy as well as maternal deaths from COVID-19, indicating potential for severe maternal morbidity and mortality.[12-14] The case of maternal death in our series highlights the potential for the disease course to be protracted with seemingly unpredictable and abrupt deterioration in health after 10-14 days.[15]

One of the most important goals of the healthcare community during SARS-CoV-2 pandemic is identification of populations at risk for severe disease and death. Racial and ethnic disparities as risk factors for severe COVID-19 are an emerging focus of COVID-19 studies in the United States.[16-19] Our data raises concern about the role of social determinants of health and systemic inequities specific to SARS-CoV-2 transmission and healthcare access. Our findings are further supported by a recent study by Moore at al, which demonstrated a disproportionate number of COVID-19 cases among underrepresented racial/ethnic groups (with Hispanic population being the largest affected group) in COVID-19 pandemic hotspots.[20] We demonstrate that pre-pregnancy obesity is associated with more severe COVID-19, which is consistent with prior studies in non-pregnant adults and a small study of pregnant women.[13,21]

In non-pregnant adults, higher D-dimer levels are associated with increased risk of critical COVID-19 course and death.[22,23] Anticoagulation, guided by D-dimer levels, has been shown to decrease mortality in this population.[24] In both complicated and uncomplicated pregnancies, however, D-dimer levels are known to increase above baseline, though reference ranges are inconsistent.[25] Our study presents novel data on D-dimer trends in SARS-CoV-2 positive symptomatic and asymptomatic women in relation to delivery. CRP has emerged as another independent predictor of adverse outcomes in non-pregnant COVID-19 patients [26]. Our data suggests that D-dimer may not be helpful in determining disease severity in a pregnant and peripartum COVID-19 population. Its use for anticoagulation guidance needs to be further evaluated. Similar to D-dimer, there are no well-established reference ranges for CRP in pregnancy and there are limited data for the use of this parameter in pregnant COVID-19 positive women.[27] Our data suggest that admission CRP values in antepartum women may emerge as a more helpful in predicting disease severity.

Clinical and Research Implications

Overrepresentation of Hispanic women in our SARS-CoV-2 positive cohort and concern for increased severity of COVID-19 disease in this group indicates an urgent need to further characterize and address the causes of these disparities. Additional larger-scale studies are needed to address the mounting evidence that racial and ethnic disparities are central to the myriad factors (e.g. health care access, housing, and ability to socially distance) that lead to the unequal distribution of SARS-CoV-2 infection and COVID-19 severity and mortality seen throughout the United States.[16]

The CDC guidelines include only severe obesity (BMI >40 mg/m^2) as a risk factor for severe illness in the non-pregnant population while our study links pre-pregnancy BMI of ≥30 kg/m^2 with worse clinical course during pregnancy.[28] The current ACOG-SMFM COVID-19 guidelines do not list obesity as a comorbidity placing pregnant women at risk for more severe disease.[29] Given our findings, consideration should be made to include all classes of obesity as a risk factor in pregnancy for progression to moderate and severe disease.

Lastly, larger studies are required to review possible association between SARS-CoV-2 infection and HDP.

Strengths and Limitations

Our study was performed in a diverse health care system consisting of academic and community hospitals with a racially and ethnically diverse population; however, the study is limited to a single geographic location and may not be generalizable to other regions of the country with different patient populations and prevalence of SARS-CoV-2. Additionally, this population is heterogenous with both symptomatic and asymptomatic women being tested for SARS-CoV-2. We acknowledge that many women with symptoms were likely never tested and

new commercial tests performed outside of hospital labs emerged during the course of this study, the results of which may have not been incorporated in the EHR and identified for review. Furthermore, testing guidelines as well as management strategies evolved during the study period, thus, contributing to the variation in clinical decision making. WHO COVID-19 severity assignment criteria were used for this study as this classification system was the only one explicitly applicable for pregnancy at the time. Furthermore, we adjusted the oxygen saturation criterion for severe disease from < 90% on room air in non-pregnancy to < 95% in pregnancy.[30] The racial and ethnic composition of the tested population may not be an accurate representation of the overall pregnant population. We were unable to compare the rates of HDP in COVID-19 positive and negative patients as we had limited access to the data on the latter group. CRP value comparisons between COVID-19 severity groups were limited by small sample size. We were unable to perform a multivariate analysis to assess for confounding due to small sample size. Lastly, unlike other literature, we failed to demonstrate associations between pre-existing hypertension and diabetes with worse COVID-19 course; this may be due to a relatively small sample size.[31] Larger registry studies are needed to examine the risk factors associated with COVID-19 progression in pregnancy.

Conclusions

This study demonstrates that the majority of pregnant women with COVID-19 remain either asymptomatic or have mild disease; however, severe illness and death can occur. Pre-pregnancy obesity was associated with an increased risk of severe illness. Further, the Hispanic population in this cohort appeared to be at increased risk for severe illness. Large-scale studies are required to develop better risk stratification strategies for COVID-19 in pregnancy.

References:

1. Johns Hopkins University Coronavirus resource center. COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University. 2020; https://coronavirus.jhu.edu/map
2. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. COVID-19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *American journal of obstetrics & gynecology MFM.* 2020:100118.
3. Li N, Han L, Peng M, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2020.
4. American Academy of Pediatrics. FAQs: Management of Infants Born to Mothers with Suspected or Confirmed COVID-19. 2020; https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/faqs-management-of-infants-born-to-covid-19-mothers/.
5. WHO. Clinical management of COVID-19. Interim guidance. 2020; https://www.who.int/publications-detail/clinical-management-of-covid-19.
6. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstetrics and gynecology.* 2020;135(6):e237-e260.
7. Hosier H, Farhadian SF, Morotti RA, et al. SARS-CoV-2 infection of the placenta. *The Journal of clinical investigation.* 2020.
8. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. *The Lancet. Infectious diseases.* 2020;20(5):559-564.
9. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *American journal of obstetrics and gynecology.* 2004;191(1):292-297.
10. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi.* 2019;52(3):501-503.
11. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *American journal of obstetrics and gynecology.* 2020.
12. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal Death Due to COVID-19 Disease. *American journal of obstetrics and gynecology.* 2020.
13. Pierce-Williams RAM, Burd J, Felder L, et al. Clinical course of severe and critical COVID-19 in hospitalized pregnancies: a US cohort study. *American journal of obstetrics & gynecology MFM.* 2020:100134.
14. Blitz MJ, Rochelson B, Minkoff H, et al. Maternal Mortality Among Women with COVID-19 Admitted to the Intensive Care Unit. *American journal of obstetrics and gynecology.* 2020.
15. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *New England Journal of Medicine.* 2020.

16. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and Racial/Ethnic Disparities. *Jama.* 2020.
17. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. *MMWR. Morbidity and mortality weekly report.* 2020;69(15):458-464.
18. Wadhera RK, Wadhera P, Gaba P, et al. Variation in COVID-19 Hospitalizations and Deaths Across New York City Boroughs. *Jama.* 2020.
19. Goldfarb IT, Clapp MA, Soffer MD, et al. Prevalence and Severity of Coronavirus Disease 2019 (COVID-19) Illness in Symptomatic Pregnant and Postpartum Women Stratified by Hispanic Ethnicity. *Obstetrics & Gynecology.* 9000;Publish Ahead of Print.
20. Moore JT, Ricaldi JN, Rose CE, et al. Disparities in Incidence of COVID-19 Among Underrepresented Racial/Ethnic Groups in Counties Identified as Hotspots During June 5-18, 2020 - 22 States, February-June 2020. *MMWR. Morbidity and mortality weekly report.* 2020;69(33):1122-1126.
21. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama.* 2020.
22. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England).* 2020;395(10229):1054-1062.
23. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ (Clinical research ed.).* 2020;369:m1966.
24. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of thrombosis and haemostasis : JTH.* 2020;18(5):1094-1099.
25. Baboolall U, Zha Y, Gong X, Deng DR, Qiao F, Liu H. Variations of plasma D-dimer level at various points of normal pregnancy and its trends in complicated pregnancies: A retrospective observational cohort study. *Medicine.* 2019;98(23):e15903.
26. Luo X, Zhou W, Yan X, et al. Prognostic value of C-reactive protein in patients with COVID-19. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2020.
27. Pereira A, Cruz-Melguizo S, Adrien M, Fuentes L, Marin E, Perez-Medina T. Clinical course of Coronavirus Disease-2019 (COVID-19) in pregnancy. *Acta obstetricia et gynecologica Scandinavica.* 2020.
28. Centers for Disease Control and Prevention. People Who Are at Higher Risk for Severe Illness. 2020; https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html.
29. The American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine. Outpatient Assessment and Management for Pregnant Women With Suspected or Confirmed Novel Coronavirus (COVID-19). 2020; https://www.smfm.org/covidclinical.

30. Society for Maternal-Fetal Medicine: Management Considerations for Pregnant Patients With COVID-19. 2020; https://www.smfm.org/covidclinical.
31. Andrikopoulou M, Madden N, Wen T, et al. Symptoms and Critical Illness Among Obstetric Patients With Coronavirus Disease 2019 (COVID-19) Infection. *Obstetrics and gynecology.* 2020.

436 **Table 1. Patient characteristics, co-morbidities and COVID-19 severity.**
437

Characteristics	TOTAL	COVID-19 SEVERITY				P value
		Asymptomatic	Mild	Moderate	Severe/ critical	
	141 (100%)	44 (31.2%)	82 (58.2%)	9 (6.4%)	6 (4.3%)	
Age (continuous)						
Median (IQR)	30 (25-34)	30 (24-33.5)	30 (25-35)	34 (30-35)	30.5 (23-35)	0.62
Age (categorical)						
<25	32 (22.7)	13 (29.5)	16 (19.5)	1 (11.1)	2 (33.3)	0.40
25<35	74 (52.5)	23 (52.3)	45 (54.9)	5 (55.6)	1 (16.7)	
35<40	27 (19.1)	6 (13.6)	15 (18.3)	3 (33.3)	3 (50.0)	
40+	8 (5.7)	2 (4.6)	6 (7.3)	0 (0.0)	0 (0.0)	
Race-ethnicity						
Hispanic	61 (43.9)	17 (38.6)	33 (40.7)	7 (87.5)	4 (66.7)	0.19
White, non-Hispanic	38 (27.3)	13 (29.6)	25 (30.9)	0 (0.0)	0 (0.0)	
Black, non-Hispanic	30 (21.6)	9 (20.5)	19 (23.5)	1 (12.5)	1 (16.7)	
Asian and other	10 (7.2)	5 (11.4)	4 (4.9)	0 (0.0)	1 (16.7)	
Ethnicity						
Hispanic	61 (43.9)	17 (38.6)	33 (40.7)	7 (87.5)	4 (66.7)	0.04
Non-Hispanic	78 (56.1)	27 (61.4)	48 (59.3)	1 (12.5)	2 (33.3)	
Insurance						
Commercial	54 (40.6)	20 (50.0)	29 (37.2)	4 (44.4)	1 (16.7)	0.32
State	60 (45.1)	18 (45.0)	33 (42.3)	4 (44.4)	5 (83.3)	
Hospital program	15 (11.3)	1 (2.5)	13 (16.7)	1 (11.1)	0 (0.0)	
None, self-pay	4 (3.0)	1 (2.5)	3 (3.8)	0 (0.0)	0 (0.0)	
Marital status						
Married with partner	67 (47.9)	23 (53.5)	36 (43.9)	4 (44.4)	4 (66.2)	0.58
Single, widowed, other	73 (52.1)	20 (46.5)	46 (56.1)	5 (55.6)	2 (33.3)	
Known COVID-19 exposure						
No	56 (40.3)	17 (38.6)	34 (41.5)	1 (14.3)	4 (66.7)	0.04
Yes	48 (34.5)	11 (25.0)	32 (39.0)	5 (71.4)	0 (0.0)	
Unknown	35 (25.2)	16 (36.4)	16 (19.5)	1 (14.3)	2 (33.3)	
Timing of COVID-19 diagnosis						
1st trimester	11 (7.8)	0 (0.0)	10 (12.2)	0 (0.0)	1 (16.7)	NAC
2nd trimester	37 (26.2)	4 (9.1)	29 (35.4)	1 (11.1)	3 (50.0)	

3rd trimester	35 (24.8)	2 (4.5)	25 (30.5)	7 (77.8)	1 (16.7)	
Delivery admission	51 (36.2)	37 (84.1)	12 (14.6)	1 (11.1)	1 (16.7)	
Postpartum	7 (5.0)	1 (2.3)	6 (7.3)	0 (0.0)	0 (0.0)	
Gestational age at delivery (n=77)						
Median (IQR)	39 (38-40)	39 (38-39)	39 (38-40)	38.5 (38-40)	30 (22-38)	0.35
Gestational age at diagnosis-antepartum (n=132)						
Median (IQR)	35 (22-38.5)	39 (38-39)	27.5 (17-36)	35 (30-36)	26 (22-31)	<0.001
Any comorbidity						
No	84 (59.6)	31 (70.4)	45 (54.9)	6 (66.7)	2 (33.3)	0.19
Yes	57 (40.4)	13 (29.6)	37 (45.1)	3 (33.3)	4 (66.7)	
Obesity (pre-pregnancy BMI >=30)						
<30	79 (59.0)	30 (71.4)	46 (57.5)	3 (42.9)	0 (0.0)	0.01
>=30	55 (41.0)	12 (28.6)	34 (42.5)	4 (57.1)	5 (100.0)	
Obesity (pre-pregnancy BMI)						
<30	79 (59.0)	30 (71.4)	46 (57.5)	3 (42.9)	0 (0.0)	<0.01
30<35	22 (16.4)	5 (11.9)	14 (17.5)	1 (14.3)	2 (40.0)	
35<40	18 (13.4)	2 (4.8)	10 (12.5)	3 (42.9)	3 (60.0)	
40+	15 (11.7)	5 (11.9)	10 (12.5)	0 (0.0)	0 (0.0)	
Pre-gestational diabetes						
No	132 (95.0)	42 (97.7)	76 (93.8)	9 (100.0)	5 (83.3)	0.35
Yes (pre-pregnancy or early diagnosis)	7 (5.0)	1 (2.3)	5 (6.2)	0 (0.0)	1 (16.7)	
Chronic hypertension						
No	126 (90.0)	40 (90.9)	75 (91.5)	7 (87.5)	4 (66.7)	0.21
Yes	14 (10.0)	4 (9.1)	7 (8.5)	1 (12.5)	2 (33.3)	
Heart disease						
No	134 (95.0)	43 (97.7)	76 (92.7)	9 (100.0)	6 (100.0)	0.74
Yes	7 (5.0)	1 (14.3)	6 (7.3)	0 (0.0)	0 (0.0)	
Asthma						
No	122 (87.1)	40 (93.0)	70 (85.4)	8 (88.9)	4 (66.7)	0.20
Yes	18 (12.9)	3 (7.0)	12 (14.6)	1 (11.1)	2 (33.3)	
Smoking						
Never	113 (81.3)	38 (90.5)	64 (78.1)	6 (66.7)	5 (83.3)	0.19
Current or former	19 (13.7)	3 (7.1)	13 (15.8)	3 (33.3)	0 (0.0)	
Unknown	7 (5.0)	1 (2.4)	5 (6.1)	0 (0.0)	1 (16.7)	

Numbers may not add to 141 due to missing values; percentages may not add to 100 due to rounding. IQR, interquartile range. BMI, body mass index. NAC, not able to calculate due to low numbers.

438
439
440
441 **Table 2. Pregnancy and neonatal outcomes in COVID-19 positive women.**
442

Pregnancy outcomes	**n (%)**
Pregnancy resolved since diagnosis	80 (56.7)
Type of pregnancy outcome (n=80)	
Pregnancy termination	4 (5.0)
Spontaneous	2 (50.0)
Elective, not medically indicated	1 (25.0)
Medically indicated (COVID-19 related)	1 (25.0)
Livebirths	76 (95.0)
Preterm birth	3 (3.9)
Spontaneous preterm birth	2 (66.7)
Medically indicated preterm birth	1 (33.3)
COVID-19 related	0 (0.0)
Term delivery	73 (96.1)
Spontaneous	40 (54.8)
Scheduled cesarean delivery	6 (8.2)
Medically indicated	27 (37.0)
COVID-19 related	0 (0.0)
Mode of delivery (n=77)	
Vaginal	52 (67.5)
Cesarean section by type	24 (31.2)
Indicated by COVID-19	1 (4.2)
Previous cesarean delivery, no labor	6 (25.0)
Fetal distress	8 (33.3)
Failed induction	1 (4.2)
Arrest of dilation	1 (4.2)
Arrest of descent	0 (0.0)
Malpresentation	4 (16.7)
Other, NA	3 (12.5)
Dilation and Evacuation	1 (1.3)
Hypertensive disorders of pregnancy (n=77)	
Any	17 (22.1)

Gestational hypertension	4 (5.2)
Preeclampsia without severe features	4 (5.2)
Preeclampsia with severe features	8 (10.4)
HELLP	1 (1.3)
Gestational diabetes (n=75)	
None	68 (90.7)
A1	3 (4.0)
A2	4 (5.3)
Neonatal outcomes (n=73)	
Newborn SARS-CoV-2 test of nasopharyngeal swabs	
Negative	60 (82.2)
Positive	0 (0)
Not tested	13 (17.8)
Neonatal intensive care unit admission	
No	63 (86.3)
Admission COVID19 related	0 (0.0)
Admission not COVID19 related	10 (13.7)

FIGURE LEGENDS

Figure 1. Timing of diagnosis, clinical course and pregnancy outcomes in COVID-19 positive women.

Figure 2. Symptom frequency among different groups of symptomatic COVID-19 positive patients. a. Overall symptom frequency in the symptomatic group. b. Symptom frequency in symptomatic group stratified by the severity of COVID-19 disease. The p-values were based on Fisher exact test of association between the 3-level severity and dichotomous symptoms. Symptoms with P-value <0.05 were marked with *.

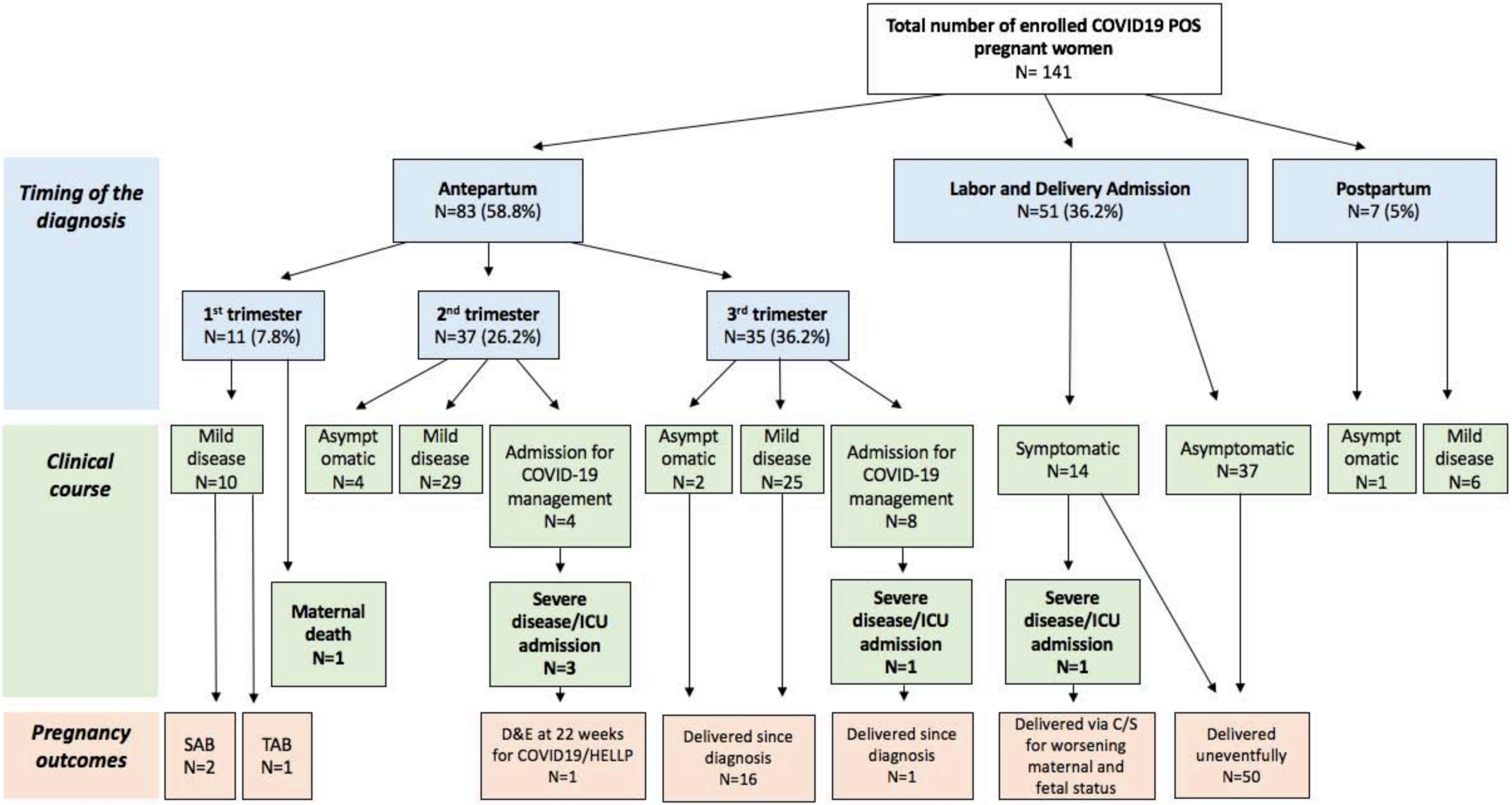
Figure 3. Laboratory trends in symptomatic and asymptomatic COVID-19 positive women admitted antepartum or for delivery. a. *D-dimer* trends in asymptomatic and symptomatic COVID-19 patients during delivery encounter. **b**. *D-dimer* trends in COVID-19 positive patients admitted antepartum (for COVID-19 and non-COVID-19 indications), who were discharged undelivered. **c.** *CRP* trends in asymptomatic and symptomatic COVID-19 patients during delivery encounter. Marked lines indicate cesarean delivery. **d.** *CRP* trends in COVID-19 positive patients admitted antepartum (for COVID-19 and non-COVID-19 indications), who

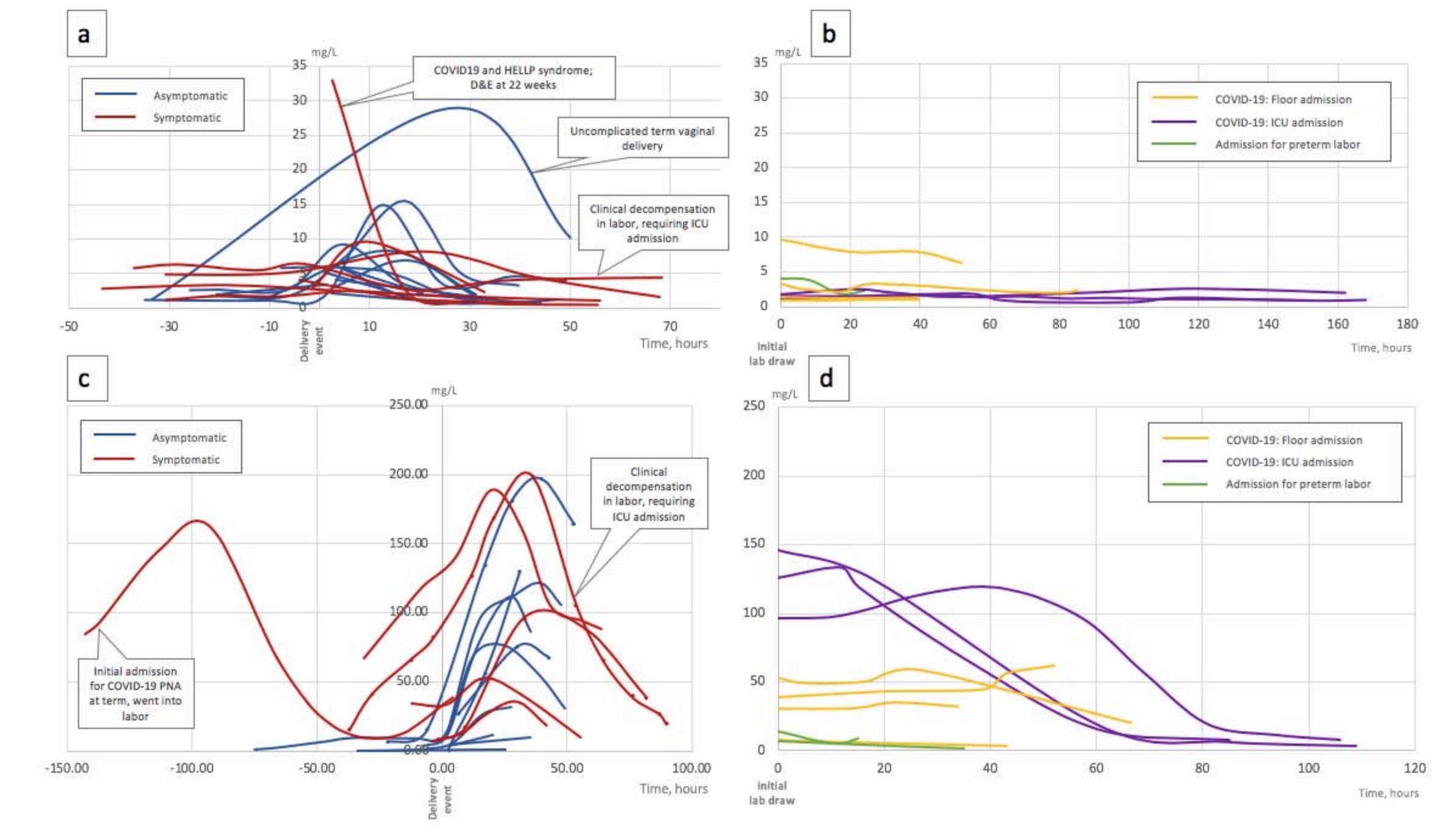
were discharged undelivered. D&E, dilation and evacuation; PNA, pneumonia; ICU, intensive care unit.

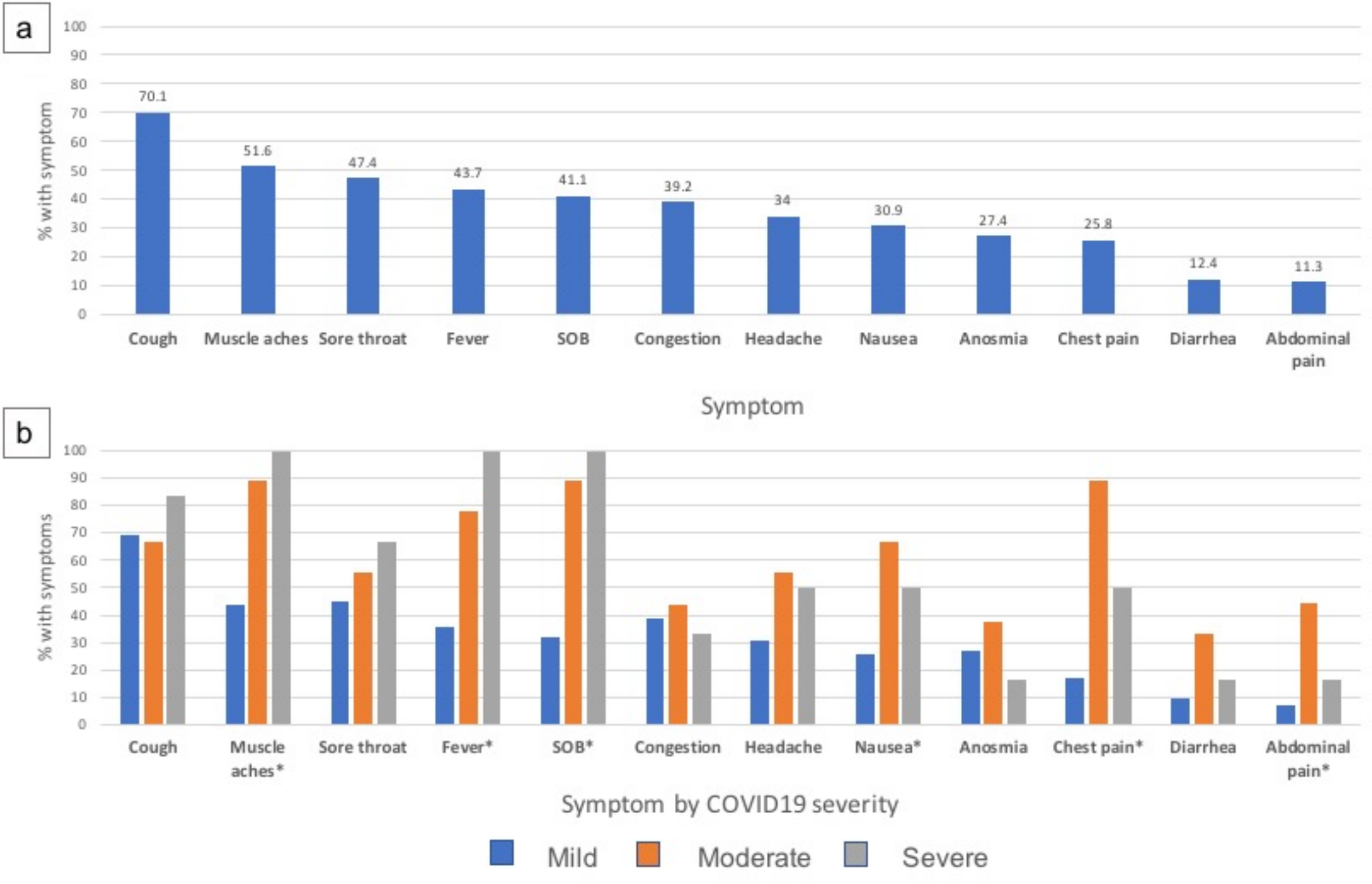
Supplemental Figure 1. Yale-New Haven Hospital System Outpatient Management Guidelines of SARS-CoV-2 Positive Pregnant Women.

HIGHLIGHTS:

- The majority of pregnant women with SARS-CoV-2 infection are asymptomatic or have mild disease
- However, severe COVID-19 disease and maternal death occur
- Pregnant Hispanic women have higher disease rate and increased severity of COVID-19
- Obesity is associated with increased COVID-19 severity in pregnancy


Total number of enrolled COVID19 POS pregnant women
N= 141
Timing of the diagnosis
Antepartum
N=83 (58.8%)
Labor and Delivery Admission
N=51 (36.2%)
Postpartum
N=7 (5%)
1st trimester
N=11 (7.8%)
2nd trimester
N=37 (26.2%)
3rd trimester
N=35 (36.2%)
Clinical course
Mild disease
N=10
Asympt omatic
N=4
Mild disease
N=29
Admission for COVID-19 management
N=4
Asympt omatic
N=2
Mild disease
N=25
Admission for COVID-19 management
N=8
Symptomatic
N=14
Asymptomatic
N=37
Asympt omatic
N=1
Mild disease
N=6
Maternal death
N=1
Severe disease/ICU admission
N=3
Severe disease/ICU admission
N=1
Severe disease/ICU admission
N=1
Pregnancy outcomes
SAB
N=2
TAB
N=1
D&E at 22 weeks for COVID19/HELLP
N=1
Delivered since diagnosis
N=16
Delivered since diagnosis
N=1
Delivered via C/S for worsening maternal and fetal status
Delivered uneventfully
N=50


a
mg/L
Asymptomatic
Symptomatic
COVID19 and HELLP syndrome; D&E at 22 weeks
Uncomplicated term vaginal delivery
Clinical decompensation in labor, requiring ICU admission
Delivery event
Time, hours
b
mg/L
COVID-19: Floor admission
COVID-19: ICU admission
Admission for preterm labor
Initial lab draw
Time, hours
c
mg/L
Asymptomatic
Symptomatic
Clinical decompensation in labor, requiring ICU admission
Initial admission for COVID-19 PNA at term, went into labor
Delivery event
Time, hours
d
mg/L
COVID-19: Floor admission
COVID-19: ICU admission
Admission for preterm labor
Initial lab draw
Time, hours


a
% with symptom
100
90
80
70
60
50
40
30
20
10
0
70.1
51.6
47.4
43.7
41.1
39.2
34
30.9
27.4
25.8
12.4
11.3
Cough
Muscle aches
Sore throat
Fever
SOB
Congestion
Headache
Nausea
Anosmia
Chest pain
Diarrhea
Abdominal pain
Symptom
b
% with symptoms
Cough
Muscle aches*
Sore throat
Fever*
SOB*
Congestion
Headache
Nausea*
Anosmia
Chest pain*
Diarrhea
Abdominal pain*
Symptom by COVID19 severity
Mild
Moderate
Severe