Title: Clinical Characteristics of 46 Pregnant Women with a SARS-CoV-2 Infection in Washington State

Authors:

Erica M. LOKKEN, PhD, MS, Departments of Global Health and Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Christie L. WALKER, MD, MPH, MultiCare Health System, Tacoma, Washington, United States of America

Shani DELANEY, MD, Department of Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Alisa KACHIKIS, MD, MS, Department of Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Nicole M. KRETZER, MD, PhD, Department of Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Anne ERICKSON, MD, Department of Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Rebecca RESNICK, PhD, Medical Scientist Training Program, School of Medicine, University of Washington, Seattle, Washington, United States of America

Jeroen VANDERHOEVEN, MD, (1) Swedish Maternal Fetal Specialty Center, Swedish Medical Center, Seattle, Washington, United States of America, (2) Obstetrix Medical Group, Seattle, Washington, United States of America

Joseph K. HWANG, MD, Department of Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Nena BARNHART, MD, Department of Obstetrics and Gynecology, PeaceHealth St. Joseph's Medical Center, Bellingham, Washington, United States of America

Jasmine RAH, BA, School of Medicine, University of Washington, Seattle, Washington, United States of America

Stephen A. MCCARTNEY, MD, PhD, Department of Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Kimberly K. MA, MD, Department of Obstetrics & Gynecology, University of Washington, Seattle, Washington, United States of America

Emily M. HUEBNER, MS, School of Medicine, University of Washington, Seattle, Washington, United States of America

Chad THOMAS, MD, PhD, Department of Obstetrics and Gynecology, PeaceHealth St. Joseph's Medical Center, Bellingham, Washington, United States of America

Jessica S. SHENG, MD, MultiCare Maternal Fetal Medicine, Tacoma, Washington, United States of America

Bettina W. PAEK, MD, (1) Eastside Maternal Fetal Medicine, EvergreenHealth Medical Center, Kirkland, Washington, United States of America, (2) Obstetrix of Washington, Bellevue, Washington, United States of America

Kristin RETZLAFF, RN, Quality Department, EvergreenHealth Medical Center, Kirkland, Washington, United States of America

Carolyn R. KLINE, MD, MPH, (1) Eastside Maternal Fetal Medicine, EvergreenHealth Medical Center, Kirkland, Washington, United States of America, (2) Obstetrix of Washington, Bellevue, Washington, United States of America

Jeff MUNSON, PhD, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington, United States of America

Michela BLAIN, MD, Department of Medicine, University of Washington, Seattle, Washington, United States of America

Sylvia M. LACOURSE, MD, MPH, Departments of Medicine and Global Health, University of Washington, Seattle, Washington, United States of America

Gail DEUTSCH, MD, Seattle Children's Hospital, Seattle, Washington, United States of America

Kristina ADAMS WALDORF, MD, Departments of Obstetrics & Gynecology and Global Health, University of Washington, Seattle, Washington, United States of America

Disclosure statement: The authors report no conflict of interest. We note that Dr. Alisa Kachikis has received honoraria for work on maternal immunization through Pfizer and GlaxoSmithKline, which are outside the scope of this manuscript.

Source of financial support: This work was primarily supported by funding from the University of Washington Department of Obstetrics & Gynecology and Gift Funds. This work was also supported by the National Institute of Allergy and Infectious Diseases (grant numbers AI133976, AI145890, AI144938 and AI143265 to KAW and AI120793 to SML). Study data were managed using a REDCap electronic data capture tool hosted by the Institute of Translational Health Sciences at the University of Washington, which was supported by the National Center for Advancing Translational Sciences (UL1TR002319). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other funders.

Role of the funding source: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

This manuscript has not been presented at a meeting.

Corresponding Author: Kristina Adams Waldorf, MD, University of Washington, Box 356460, Seattle, WA 98195-6460, USA; Telephone: 206-616-5258; Fax: 206-543-3915; Email: adamsk@uw.edu

Word count (abstract): 313

Word count (main text): 3,226

Condensation:

In this Washington State case series, severe Covid-19 occurred in 15% of pregnant patients, who were typically overweight or obese pre-pregnancy or had underlying conditions.

Short Title:

Covid-19 in Pregnant Women in Washington State

AJOG at a Glance:

A. Why was the study conducted? The study was performed to determine the impact of Covid-19 on the health of pregnant women in Washington State.

B. What are the key findings? In this case series of 46 pregnant individuals with a laboratory-confirmed SARS-CoV-2 infection, nearly 15% developed severe Covid-19, which occurred primarily in overweight or obese women with underlying conditions.

C. What does this study add to what is already known? Collectively, these findings support categorizing pregnant patients as a higher risk group, particularly for those with obesity and chronic co-morbidities.

Keywords: asthma, coronavirus, Covid-19, fetal death, infection, maternal morbidity, obesity, overweight, pregnancy, SARS-CoV-2, preterm birth, respiratory insufficiency, stillbirth

ABSTRACT

Background: The impact of the coronavirus disease 2019 (Covid-19) on pregnant women is incompletely understood, but early data from case series suggest a variable course of illness from asymptomatic or mild disease to maternal death. It is unclear whether pregnant women manifest enhanced disease similar to influenza viral infection or whether specific risk factors might predispose to severe disease.

Objective: To describe maternal disease and obstetrical outcomes associated with Covid-19 disease in pregnancy to rapidly inform clinical care.

Study Design: Retrospective study of pregnant patients with a laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection from six hospital systems in Washington State between January 21, 2020 and April 17, 2020. Demographics, medical and obstetric history, and Covid-19 encounter data were abstracted from medical records.

Results: A total of 46 pregnant patients with a SARS-CoV-2 infection were identified from hospital systems capturing 40% of births in Washington State. Nearly all pregnant individuals with a SARS-CoV-2 infection were symptomatic (93.5%, n=43) and the majority were in their second or third trimester (43.5%, n=20 and 50.0%, n=23, respectively). Symptoms resolved in a median of 24 days (interquartile range 13-37). Seven women were hospitalized (16%) including one admitted to the intensive care unit. Six cases (15%) were categorized as severe Covid-19 disease with nearly all patients being either overweight or obese prior to pregnancy, asthma or other co-morbidities. Eight deliveries occurred during the study period, including a preterm birth at 33 weeks to

improve pulmonary status in a woman with Class III obesity. One stillbirth occurred of unknown etiology.

Conclusions: Nearly 15% of pregnant patients developed severe Covid-19, which occurred primarily in overweight or obese women with underlying conditions. Obesity and Covid-19 may synergistically increase risk for a medically-indicated preterm birth to improve maternal pulmonary status in late pregnancy. Collectively, these findings support categorizing pregnant patients as a higher risk group, particularly for those with chronic co-morbidities.

INTRODUCTION

The coronavirus disease of 2019 (Covid-19) has led to the largest and deadliest pandemic since the 1918 influenza pandemic. The first reported case of Covid-19 in the United States was in Washington State on January 21, 2020; the United States now has the highest rates of Covid-19 prevalence and mortality worldwide(1, 2). Covid-19 is caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), which results in a spectrum of disease ranging from asymptomatic and mild cases to respiratory failure, shock, multiorgan dysfunction and death(3).

The clinical course of Covid-19 in pregnant women is incompletely understood and there is concern for enhanced disease in some pregnant women and an increased risk for spontaneous abortion, preterm birth or morbidity/mortality in the fetus and neonate(4-8). Several case series have reported a variable course of illness in the antepartum, intrapartum, and postpartum periods(9-14). Limited reports suggesting vertical transmission underscore the potential vulnerability of the fetus and neonate(15-18). Further, the relationship between timing of infection in pregnancy and the long-term impacts on neurodevelopmental and neuropsychiatric outcomes in the children are unknown(19, 20). Many questions remain unanswered, including whether pregnancy is a high-risk state for enhanced disease in some circumstances and the impact of infection on the developing fetus and neonate.

Washington State has been on the forefront of the national Covid-19 response. It was among the first states to confirm community transmission(21) and to declare a State of

Emergency(22). In response to the pandemic, the Washington State Covid-19 in Pregnancy Collaborative was established to investigate cases among pregnant patients at major tertiary referral centers and community hospitals disproportionately impacted by the pandemic. The study objective was to describe maternal and obstetrical outcomes associated with Covid-19 disease in pregnancy to rapidly inform clinical care.

MATERIALS AND METHODS

Study Design & Study Population

We identified pregnant women (≥18 years) with laboratory-confirmed SARS-CoV-2 infections from six hospital systems in Washington State between January 21, 2020 and April 17, 2020. All pregnant patients with a positive SARS-CoV-2 test result during any trimester of pregnancy, regardless of symptoms, were included. All testing was performed using a polymerase chain reaction (PCR) test, which varied in assay design and source by institution. Participating institutions were part of the Washington State Covid-19 in Pregnancy Collaborative, representing 16 hospitals from the Seattle-Tacoma-Bellevue metropolitan area, Bellingham, Spokane and their surrounding areas. Sites included the University of Washington Hospital system (Montlake, Northwest, and Harborview campuses), Swedish Medical Center (First Hill, Ballard, Issaquah and Edmonds campuses), University of Washington Valley Medical Center, MultiCare Health System (Auburn Medical Center, Covington Medical Center, Tacoma General Hospital, Good Samaritan Hospital, Valley Hospital and Deaconess Hospital), EvergreenHealth Medical Center, and PeaceHealth-St. Joseph's Medical Center. These sites have 34,000

deliveries annually, which represent 40% of the ~86,000 deliveries each year in Washington State(23).

Patient Identification, Data Collection, and Statistical Analysis

Eligible subjects were identified at collaborating institutions by site-specific team members through electronic medical records searches using ICD10 diagnostic codes and site-specific algorithms. De-identified data were abstracted from the electronic medical records by a primary abstractor and entered into a REDCap database (Research Electronic Data Capture software, Vanderbilt University) managed by the coordinating team at the University of Washington. All data entry was confirmed by a secondary abstractor. Abstractors included University of Washington School of Medicine students, University of Washington Department of Obstetrics & Gynecology physician residents, attending obstetricians, maternal-fetal medicine specialists and an obstetrical nurse. Data collected included demographics, medical and obstetric history, SARS-CoV-2 testing and clinical encounters including symptoms, laboratory results, pulmonary imaging and hospitalization, when applicable. For patients who delivered by the time of chart abstraction, we collected data on delivery characteristics and complications. Data were summarized using proportions and medians (interquartile range, IQR). A Kaplan-Meier curve was generated to estimate days from Covid-19 associated-respiratory symptom onset to resolution. Patients with ongoing symptoms were censored at the last report of symptoms in a clinical encounter.

COVID-19 Disease Categories

We used criteria for Covid-19 disease severity previously defined in non-pregnant adults(24) and subsequently applied to pregnant women(25). Categories were defined as: 1) mild (non-pneumonia or mild pneumonia), 2) severe (dyspnea, respiratory rate ≥30 breaths/min, percutaneous oxygen saturation ≤93% on room air at rest, arterial oxygen tension over inspiratory oxygen fraction of less than 300 mmHg, and/or lung infiltrates >50% within 24 to 48 hours, and 3) critical (severe respiratory distress, respiratory failure requiring mechanical ventilation, shock, and/or multiple organ dysfunction or failure). Normal laboratory reference ranges in each trimester of pregnancy are in Table S1(26).

Placental and Fetal Histopathology

In one case, a fetal autopsy was performed with gross and histopathological evaluation of fetal tissues and the placenta. PCR testing of multiple fetal and placental tissues was performed for SARS-CoV-2 RNA and cytomegalovirus DNA using established clinical assays at the University of Washington.

Ethics Statement

This multi-site medical records review was approved by Institutional Review Boards (IRB) at the University of Washington (STUDY# 00009701, approved 03/06/2020) and Swedish Medical Center (STUDY #2020000172, approved 03/19/2020). All remaining sites entered into reliance agreements with the University of Washington IRB for study approval. Patient consent and HIPAA (Health Insurance Portability and Accountability Act) authorization were waived by the IRBs for this study using de-identified data.

Consent to publish information associated with the fetal autopsy was obtained through a study approved by the Seattle Children's Hospital IRB.

RESULTS

Patient Demographics, Co-morbidities, & Pregnancy History

A total of 46 pregnant patients with SARS-CoV-2 infections were identified during the study period with a median age of 29 years (IQR 26-34) and 26.1% (n=12) were nulliparous. One woman was pregnant with twins and the remainder had singleton pregnancies. The majority were white (60.9%, n=28) and had private insurance (58.7%, n=27). Positive SARS-CoV-2 test results were identified predominantly in second (43.5%, n=20) and third trimester (50.0%, n=23) pregnancies; only three cases were detected in first trimester pregnancies (6.5%; Figure 1). Approximately two-thirds of patients were either overweight (28.6%, n=12) or obese (35.7%, n=15) by their pre-pregnancy body mass index (BMI); two women met criteria for Class III Obesity (BMI $\geq$40). Although the majority of patients were healthy, 26.1% (n=12) had an underlying health condition(s) including type 2 diabetes (n=3), asthma (n=4), hypothyroidism (n=2), hypertension (n=2), and several less common conditions (e.g. Crohn's treated with immunosuppressive medication, seizure disorder history). Although no patients reported smoking cigarettes during pregnancy, one reported marijuana use and one endorsed alcohol use.

SARS-CoV-2 Testing & Symptoms

SARS-CoV-2 testing became increasingly available over the study period starting with facility-based and outpatient "drive through" testing stations for symptomatic individuals

and expanding to universal screening on Labor & Delivery at several medical centers. Nearly all pregnant patients (93.5%, n=43) were tested due to Covid-19-related symptoms (Table 2). The remaining three patients were asymptomatic but tested due to known exposure. Women reported a median of two symptoms (IQR 1-5), which most commonly included cough (69.8%, n=30), fever or chills (51.2%, n=22), nasal congestion (48.8%, 21) and shortness of breath (44.2%, n=19; Table 2). Loss of taste or smell was reported in 30.2% (n=13) of cases. Median time to symptom resolution was 24 days (IQR 13-37; Fig. 1 and Fig. S1). In one case, a woman with a prolonged symptomatic course of at least 37 days, sought care in the emergency room three times and was hospitalized once for respiratory symptoms. Follow-up data on symptoms were not available for three women who were asymptomatic at SARS-CoV-2 testing. No co-infections were detected in seven patients (15.2%) tested for other respiratory viruses (i.e. influenza and respiratory syncytial viruses).

Covid-19 Disease Course, Imaging, Medical Management and Hospital Admission

The majority of cases were managed as outpatients for either mild in severity (78.3%, 36/46) or asymptomatic (6.5%, 3/46) presentations. Although few outpatients underwent pulmonary imaging (12.8%, n=5/39), two women had pneumonia, but were not admitted. An additional seven pregnant patients (15.2%) were hospitalized for Covid-19, one of whom was admitted to the intensive care unit (Table 3). Six of the seven hospitalized patients met criteria for severe Covid-19 disease (24). Nearly all patients with severe disease were overweight or obese prior to pregnancy (80%, 4/5 with data) and half had asthma and obesity-associated conditions (e.g. hypertension). Three (42.9%)

hospitalized patients received Covid-19-directed medications including hydroxychloroquine and remdesivir (n=1) or remdesivir alone (n=2). Two patients received azithromycin without concomitant hydroxychloroquine; one for possible community acquired pneumonia and one in the setting of asthma exacerbation.

Laboratory testing was performed in 24 women, who were either hospitalized for Covid-19 (n=7) or managed as an outpatient (n=17); due to multiple encounters, including delivery admission, laboratory test results were evaluated from the time of Covid-19 diagnosis until delivery (Table 3, Table S2). Of the 24 patients with white blood cell measurements, eight had leukopenia (33%) using pregnancy-specific laboratory reference ranges ($<5.6 \times 10^3$ per μl; Table S1); half of these patients (4/8) were managed as outpatients. Neither creatinine nor C-reactive protein was elevated in those who had testing (creatinine, 0/21; C-reactive protein, 0/6; Table S1). Seven patients had a mildly elevated aspartate aminotransferase (AST), including five managed as outpatients (31.3%, 5/16) and two that were hospitalized (33.3%, 2/6). Lastly, a markedly elevated D-dimer was detected in one of five patients (20%) in which the test was ordered (Case 25: 4.08 ng/mL, Table 3).

The patient admitted to the intensive care unit was a young woman (20-25 years old) at 30 weeks, who presented with a one-week history of fever and cough. She was overweight prior to pregnancy (BMI 26.2) and had asthma. She was admitted to the intensive care unit due to acute respiratory failure with a percutaneous oxygen saturation as low as 82% on room air and a respiratory rate as high as 49. She received remdesivir

(6 doses), hydroxychloroquine and high flow oxygen. She was transferred out of the intensive care unit on day 3 and discharged home on day 6 (Table 3, Case 25).

Maternal-Fetal Outcomes

During the study period, 8 (17.4%) patients delivered, including seven live births and one stillbirth (Table 4). The median number of days between a positive SARS-CoV-2 test and delivery was 7.5 days (IQR 5.0-11.5). The median gestational age at delivery was 38.4 weeks (IQR 37.5-39.8). In one case, worsening respiratory status and multiple co-morbidities, including Class III obesity, led to the decision to deliver the patient preterm at 33 weeks gestation (Case 27, Table 3). Of the eight deliveries, five (62.5%) were vaginal and 3 (37.5%) were cesarean delivery. Two of the three cesarean deliveries were performed, in part, to improve maternal respiratory status due to Covid-19 disease. During the delivery admission, two women developed postpartum preeclampsia with severe features within one day of delivery; both women had elevated blood pressure, but no pre-eclampsia-associated laboratory abnormalities. In these two cases, intravenous anti-hypertensive medications were administered, but magnesium sulfate was not given due to concern for exacerbating pulmonary edema.

Details of the case resulting in a stillbirth at 38.7 weeks are described in the Supplemental Appendix. Postmortem examination of the placenta revealed severe chronic villitis, but no viral inclusions. Qualitative PCR testing of placental and fetal tissues was negative for SARS-CoV-2 and cytomegalovirus; notably, there was a delay between fetal demise and

RNA preservation for PCR analysis, which can lead to inaccurate PCR results. The etiology in this case is unclear.

COMMENT

Principal Findings

This case series of 46 pregnant patients with Covid-19 represents all known cases across six large hospital systems in Washington State from a time period when patients were mainly tested based on symptoms. Notably, one in seven pregnant patients were hospitalized for respiratory concerns and one in eight had severe Covid-19 disease. Pregnant patients with severe Covid-19 were nearly all overweight or obese prior to pregnancy and many had additional co-morbidities including asthma and hypertension. Obesity as a risk factor for severe Covid-19 in pregnancy is particularly concerning as the national prevalence of obesity was 39.7% among women of reproductive age (20–39 years old) in 2017-2018(27). Obesity is known to impair lung function through both mechanical and inflammatory pathways(28). A synergistically detrimental impact on maternal lung function may occur in the setting of multiple factors such as a Covid-19 pneumonia, obesity, asthma, and the added mechanical stress of an enlarged uterus in late pregnancy; this combination may also increase the risk for a medically-indicated preterm birth to improve maternal respiratory status.

Results in the Context of What is Known

Similar to the non-pregnant population, descriptions of the clinical course of Covid-19 disease in pregnancy have been variable (7, 17, 25). A systematic review of early case series was notable for a low rate of admission to the intensive care unit (3%), no maternal

deaths, and only one neonatal death and one intrauterine fetal demise(6). In a recent and larger case series from the Hubei province in China, the rate of severe pneumonia (7-8%) in pregnant women was not higher than the general population (15%)(7). Newer reports have highlighted critical cases in pregnant women involving respiratory failure, mechanical ventilation, maternal death, as well as obstetrical complications like preterm birth and intrauterine fetal demise(8, 17, 29-32). Our population-based case series of pregnant patients with Covid-19 from counties in Washington State with the highest burden of disease offers a unique insight into the disease course in pregnancy and identifies potential risk factors associated with severe disease. Obesity, asthma and hypertension appeared to be overrepresented in pregnant patients with severe disease in our cohort, which is similar to studies in non-pregnant adults(33, 34).

Clinical Implications

Although outpatient management of Covid-19 may be safe for most pregnant patients, the risks of Covid-19 for maternal health remains incompletely defined. There is evidence of Covid-19-associated coagulopathy and whether pregnant women would benefit from thromboprophylaxis is unknown(35). In our case series, the markedly elevated D-dimer (>4.0 μg/ml) in a pregnant woman with severe Covid-19 is significant, because levels greater than 1.0 and 2.0 μg/ml have been linked to an increased risk for Covid-19-associated mortality(36-38). Pregnant women are known to have an elevated D-dimer during pregnancy, which may be as high as 3.3 μg/ml in the second and third trimesters(39) and could predispose pregnant women to an even greater risk for Covid-19-associated thrombogenic events and mortality. Laboratory testing of D-dimer should be considered for pregnant women with Covid-19.

Pregnant women typically represent a unique and vulnerable group to infectious diseases, not only because they often have enhanced disease (i.e. influenza and hepatitis E viruses)(40), but also due to the detrimental impact on obstetrical course and neonatal outcomes. In our series, the timing of delivery for one in four women was influenced by the impact of a Covid-19 pneumonia on maternal lung function; in one case, this necessitated preterm delivery at 33 weeks. Covid-19 disease in the mother can pose a maternal-fetal dilemma, because an intervention that would benefit her (i.e. delivery to improve maternal lung function) might result in morbidity or mortality to the neonate if delivered prematurely. The rate of medically-indicated preterm birth is a critically important feature contributing to the vulnerability of pregnant women to Covid-19.

The impact of Covid-19 on resource utilization across all sites was significant and not captured by this data. Outpatient adjustments included changes such as daily symptom screening, daily calls to patients with Covid-19, notification of new visitation policies, rescheduling of appointments and conversion to new telemedicine platforms. In the hospital, limitations on the number of people providing labor support, development of new practices for universal screening before/upon admission, new construction of negative pressure rooms and frequent care coordination between obstetrics and intensive care unit teams. All of these changes resulted in increases in time, supplies and staffing that created challenges to delivery of the usual standard of maternity care. Further, the impact of quarantine on women’s lives, stress, mental health, bonding, breastfeeding and child development are critically important outcomes not captured in our case series.

Research Implications

Rigorous population-based studies are needed to identify risk factors for severe disease, the rate of adverse outcomes in pregnancy and to ascertain whether risks are increased in late pregnancy similar to influenza(41-43). Whether vertical transmission occurs remains unknown, but several case reports appear suspicious (16-18). We must also conduct follow-up studies of children exposed to SARS-CoV-2 infections in pregnancy to determine the risk for Covid-19 disease in the immediate newborn period. Both preterm birth and maternal infections may pose short- and long-term risks for the child including mortality, prematurity-related complications, and neuropsychiatric disease as an adult(19, 20, 44, 45). Finally, we must determine the impact of quarantine and mother-newborn separation on maternal health so that we can better support women in the postpartum period.

None of the pregnant women in our case series, who received medications for Covid-19 (e.g. remdesevir), were enrolled in a clinical trial, despite recommendations from the Infectious Disease Society of America that treatment of hospitalized patients with Covid-19 occur in the context of a clinical trial (46). Pregnant and breastfeeding individuals are almost universally excluded from Covid-19 clinical treatment trials, including the World Health Organization sponsored SOLIDARITY trial (ISRCTN83971151) (47). Currently, pregnant women can access both remdesivir through compassionate use and convalescent plasma (NCT04338360) through an expanded access clinical trial if they have confirmed severe Covid-19 (46, 48). In general, trials that allow inclusion of pregnant

and breastfeeding women focus on outpatient treatment trials (NCT04354428, NCT043558068) or post-exposure prophylaxis trials (NCT04308668, NCT04328961), with the exception of a convalescent plasma trial for patients hospitalized for Covid-19 (NCT04348656). It is imperative to enroll pregnant women in clinical trials testing Covid-19 therapeutics to enable development of evidence-based treatment guidelines.

Strengths and Limitations

The study's main strength is the inclusion of multiple health systems across Washington State representing counties with the highest burden of Covid-19 and approximately 40% of annual deliveries in the state. We also included both symptomatic and asymptomatic cases, as well as infections from all trimesters, allowing us to better describe the full range of infection in pregnancy. Lastly, all data were initially abstracted and/or reviewed for accuracy by clinical obstetric providers. An important study limitation is that some cases could have been missed despite the use of multiple methods of case detection at most sites. It is also likely that our case series underestimates the prevalence of asymptomatic cases, as testing resources were primarily directed towards symptomatic cases during this study period. This would bias our study towards inclusion of patients with worse clinical outcomes. Finally, other studies appear to have found more severe respiratory complications when infection occurred during the peripartum period, which was not well captured in our study as delivery outcomes were only available in eight women (6, 25, 49, 50).

Conclusions

In this population-based case series from Washington State, 15% of pregnant patients with Covid-19 were hospitalized with severe disease. Nearly all women were overweight or obese prior to pregnancy and had other important co-morbidities, such as asthma and hypertension. Our data suggests that pregnant women who have common health conditions like obesity and asthma, may be at a greater risk for severe Covid-19 disease and medically-indicated preterm delivery to improve lung function. Larger population-based studies are needed to determine whether pregnant individuals are at higher risk for severe Covid-19 illness compared to non-pregnant adult women, and to what extent obesity and other co-morbidities may enhance risk (51). Taken together, pregnant women should be considered a high risk population for severe Covid-19 disease, particularly for women in the second and third trimesters that began pregnancy overweight or obese.

ACKNOWLEDGMENTS

We would like to acknowledge several individuals for their support of this project. We thank Ms. Adrienne Meyer and Dr. Emily Guthrie with the University of Washington IRB for organizing reliance agreements with multiple study sites. Ms. Emily Begnel graciously volunteered her time to help build the REDCap database. We are thankful for the assistance provided by Ms. Bethann M. Pflugeisen for implementing site-specific algorithms to identify pregnant patients with Covid-19 in the Multicare Health system. Ms. Nicole Wothe provided administrative assistance with project management and manuscript submission. We thank Dr. Benjamin T. Bradley for providing advice associated with the fetal autopsy.

REFERENCES

1. Patel A, Jernigan DB. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak - United States, December 31, 2019-February 4, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(5):140-6.
2. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report - 83. Geneva: WHO; 12 April 2020.
3. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020.
4. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020:100107.
5. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. American journal of obstetrics and gynecology. 2020.
6. Zaigham M, Andersson O. Maternal and Perinatal Outcomes with COVID-19: a systematic review of 108 pregnancies. Acta obstetricia et gynecologica Scandinavica. 2020.
7. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: A report based on 116 cases. American journal of obstetrics and gynecology. 2020.
8. Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, et al. Second-Trimester Miscarriage in a Pregnant Woman With SARS-CoV-2 Infection. JAMA : the journal of the American Medical Association. 2020.
9. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809-15.
10. Li N, Han L, Peng M, Lv Y, Ouyang Y, Liu K, 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.
11. Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, 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.
12. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect. 2020.
13. Chen S, Liao E, Cao D, Gao Y, Sun G, Shao Y. Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia. J Med Virol. 2020.
14. Breslin N, Baptiste C, Miller R, Fuchs K, Goffman D, Gyamfi-Bannerman C, et al. COVID-19 in pregnancy: early lessons. American Journal of Obstetrics & Gynecology MFM. 2020:100111.
15. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. JAMA : the journal of the American Medical Association. 2020.
16. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. JAMA : the journal of the American Medical Association. 2020.
17. Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. Severe COVID-19 during Pregnancy and Possible Vertical Transmission. American journal of perinatology. 2020.
18. Lamouroux A, Attie-Bitach T, Martinovic J, Leruez-Ville M, Ville Y. Evidence for and against vertical transmission for SARS-CoV-2 (COVID-19). 2020.

19. Al-Haddad BJS, Jacobsson B, Chabra S, Modzelewska D, Olson EM, Bernier R, et al. Long-term Risk of Neuropsychiatric Disease After Exposure to Infection In Utero. JAMA Psychiatry. 2019.
20. Al-Haddad BJS, Oler E, Armistead B, Elsayed NA, Weinberger DR, Bernier R, et al. The fetal origins of mental illness. American journal of obstetrics and gynecology. 2019;221(6):549-62.
21. Geographic Differences in COVID-19 Cases, Deaths, and Incidence — United States, February 12–April 7, 2020. . MMWR Morb Mortal Wkly Rep
22. Proclamation by the Governor; 20-05. . Olympia, Washington: State of Washington Office of the Governor; 2020.
23. CDC Wonder Online Databases [Available from: https://wonder.cdc.gov/.
24. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA : the journal of the American Medical Association. 2020.
25. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, 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. Am J Obstet Gynecol MFM. 2020:100118.
26. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114(6):1326-31.
27. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. NCHS Data Brief. No. 360. February, 2020.
28. Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med. 2018;12(9):755-67.
29. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, Seferovic MD, Kazemi Aski S, Arian SE, et al. Maternal Death Due to COVID-19 Disease. American journal of obstetrics and gynecology. 2020.
30. Karami P, Naghavi M, Feyzi A, Aghamohammadi M, Novin MS, Mobaien A, et al. Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings. Travel Med Infect Dis. 2020:101665.
31. Hirshberg A, Kern-Goldberger AR, Levine LD, Pierce-Williams R, Short WR, Parry S, et al. Care of critically ill pregnant patients with COVID-19: a case series. American journal of obstetrics and gynecology. 2020.
32. Pierce-Williams RAM, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, et al. Clinical course of severe and critical COVID-19 in hospitalized pregnancies: a US cohort study. Am J Obstet Gynecol MFM. 2020.
33. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-5.
34. Dietz W, Santos-Burgoa C. Obesity and its Implications for COVID-19 Mortality. Obesity (Silver Spring). 2020.
35. di Renzo GC, Giardina I. Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and thromboprophylaxis. American journal of obstetrics and gynecology. 2020.
36. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
37. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020.

38. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
39. Gutierrez Garcia I, Perez Canadas P, Martinez Uriarte J, Garcia Izquierdo O, Angeles Jodar Perez M, Garcia de Guadiana Romualdo L. D-dimer during pregnancy: establishing trimester-specific reference intervals. Scand J Clin Lab Invest. 2018;78(6):439-42.
40. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211-8.
41. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol. 1998;148(11):1094-102.
42. Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2007;176(4):463-8.
43. Schanzer DL, Langley JM, Tam TW. Influenza-attributed hospitalization rates among pregnant women in Canada 1994-2000. J Obstet Gynaecol Can. 2007;29(8):622-9.
44. Preterm Birth: Causes, Consequences, and Prevention. Behrman RE, Stith Butler A, editors. Washington, D.C.: The National Academies Press; 2006.
45. Ward RM, Beachy JC. Neonatal complications following preterm birth. BJOG. 2003;110 Suppl 20:8-16.
46. Bimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 2020 [updated 04/11/2020. Available from: https://www.idsociety.org/COVID19guidelines.
47. LaCourse SM, John-Stewart G, Adams Waldorf KM. Importance of inclusion of pregnant and breastfeeding women in COVID-19 therapeutic trials. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.
48. Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19 [Available from: https://www.uscovidplasma.org/pdf/COVID-19%20Plasma%20EAP.pdf.
49. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis. 2008;14(1):95-100.
50. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. American journal of obstetrics and gynecology. 2004;191(1):292-7.
51. Buekens P, Alger J, Bréart G, Cafferata ML, Harville E, Tomasso G. A call for action for COVID-19 surveillance and research during pregnancy. Lancet Glob Health. 2020.

589 **Table 1. Demographics, Co-morbidities, and Pregnancy History for 46 Pregnant**
590 **Patients with SARS-CoV-2 Infections**
591

Characteristic	Patients (N=46)*
Demographics	
Age	29 (26-34)
Race	
Asian	2 (4.3)
Native Hawaiian or Other Pacific Islander	1 (2.2)
Black or African American	3 (6.5)
White	28 (60.9)
Multiracial	1 (2.2)
Other	2 (4.3)
Unknown / Not Reported	9 (19.6)
Ethnicity	
Hispanic or Latino	11 (23.9)
Not Hispanic or Latino	33 (71.7)
Unknown / Not Reported	2 (4.3)
Type of Insurance at diagnosis	
Public	18 (39.1)
Private	27 (58.7)
Unknown	1 (2.2)
Pre-pregnancy Existing Co-Morbidities	

Type 2 diabetes	3 (6.5)
Asthma	4 (8.7)
Hypothyroidism	3 (6.5)
Hypertension	2 (4.3)
Other co-morbidities[†]	5 (10.9)
Pre-pregnancy BMI[‡]	
Underweight (<18.5)	1 (2.4)
Normal (18.5-24.9)	14 (33.3)
Overweight (25.0-29.9)	12 (28.6)
Obese (≥30.0)	15 (35.7)
Pregnancy History	
Gravidity	2.0 (2.0-5.0)
Parity	1.0 (0.0-2.0)
History of preterm birth	3 (6.5%)

592

[*] Characteristics summarized as n(%) or median(IQR).

[†] Other comorbidities included Crohn's disease with immunosuppressive therapy (n=1); heart valve repair (n=1); Papillary thyroid carcinoma w/ thyroidectomy (n=1); seizure disorder (n=2)

[‡] Only available for 42 patients. Pre-pregnancy weight or weight prior to 12 weeks gestational age was used if pre-pregnancy weight not available. For one patient, their 14 weeks of gestation weight was used to calculate pre-pregnancy BMI.

TABLE 2. Covid-19 Symptoms at First Positive SARS-CoV-2 Test

Characteristic	Patients (N=46)*
Symptomatic prior to (or at) first positive test	43 (93.5%)
Among Symptomatic (n=43):	
Gestational age at symptom onset (weeks)	27.0 (21.0-33.9)
Number of symptoms reported	2 (1-5)
Reported Symptoms†:	
Cough	30 (69.8%)
Subjective fever or chill	22 (51.2%)
Nasal congestion	21 (48.8%)
Shortness of breath/dyspnea	19 (44.2%)
Headache	14 (32.6%)
Loss of taste or smell	13 (30.2%)
Myalgia	13 (30.2%)
Fatigue	12 (27.9%)
Sore throat	12 (27.9%)
Other symptom‡	10 (23.3%)
Nausea or Vomiting	5 (11.6%)
Diarrhea	3 (7.0%)
Days between symptom onset to resolution§	24 (13, 37)

[*] Characteristics summarized as n (%) or median (IQR).

[†] No significant difference ($p<0.05$) by trimester of infection for any reported symptom. One patient was missing symptom data for the day of positive testing, but symptom data were available and included for a subsequent Covid-19 associated encounter.

[‡] Chest pain or tightness n=5, dizziness n=1, night sweats n=1, tachycardia n=1, epigastric pain n=1, right upper quadrant pain n=1

[§] Estimated by generating a Kaplan-Meier curve to incorporate censoring.

TABLE 3. Clinical Features of Pregnant Patients with Covid-19 Associated Hospital Admissions

Characteristics	Case Number						
	12	**37**	**27**	**25**	**19**	**16**	**31**
Medical History							
Age Group*	30-35	30-35	30-35	20-25	20-25	30-35	30-35
Existing Co-morbidities	None	Prior smoker	Asthma, hypertension, hypothyroidism, Crohn's disease on immuno-suppressive medication	Asthma	Asthma, hypertension	Type 2 diabetes, hypertension	None
Pregnancy Complications	Overweight	Asymmetric IUGR (concern prior to Covid19)	Class III obesity	Overweight	Class II obesity	Class III obesity	None
Pre-Pregnancy BMI	26.3	26.2†	48.9	26.2	35.7	42.4	23.1
SARS-CoV-2 Testing							
Gestational Age at Symptom Onset (weeks)	22.3	35.1	31.4	28.9	25	23	33.9

Gestational Age at First Positive Test (weeks)	22.7	35.9	31.9	29.4	25.3	23.7	34.1
Hospitalization							
Timing							
Gestational Age at Hospitalization(s)	23.6‡	36.3	33.0	30.0	26.0	23.7	35.0
Number of Days Hospitalized	1	2	4	6, ICU for 3 days	8	4	3
Vital Signs							
Highest Respiratory Rate (breaths/min)	20	22	32	49	28	28	32
Lowest Oxygen Saturation (%)	96	94	96	82	92	95	92
Highest Temperature (°C)	37.0	38.0	37.2	37.3	38.4	38.8	37.7
Severity							
Severe Case?	Yes, dyspnea	Yes, dyspnea and infiltrates on CXR	Yes, RR ≥30	Yes, RR ≥30, oxygen saturation ≤93%	Yes, oxygen saturation ≤93%	No	Yes, RR≥30 oxygen saturation ≤93%
Pulmonary Imaging	Chest CT at GA 26.1 (normal)	CXR at GA 36.3 with pulmonary infiltrates	CXR at GA 33.0 with bilateral consolidations	CXR at GA 29.4 & 30.0 with bilateral	CXR at GAs 25.3 (normal); 26.1 & 26.4 with	CXR at GA 23.7 with unilateral consolidation	CXR at GA 35.0 with patchy opacities

				consolidations, linear opacities	bilateral consolidations		
Covid-19 Treatment	None	None	Remdesivir	Remdesivr, Hydroxy-chloroquine	Azithromycin & oral prednisone (asthma)	Remdesivir, Azithromycin & Ceftriaxone (pneumonia)	Pulmonary vasodilator
Respiratory Support	Nasal cannula	Nasal cannula	None	High flow nasal cannula	Nasal cannula	Nasal cannula	None
Delivery status at discharge?	Pregnant	Pregnant	Delivered by CS at GA 33.0; worsening respiratory status	Pregnant	Pregnant	Pregnant	Pregnant
Laboratory Results During Admission							
Lowest Hematocrit (%)	34.0	34.0	30.0	30.7	31.5	31.8	32.0
Lowest Platelets (10^3 µL)	196	128	118	171	241	112	197
Lowest WBC Count (10^3 µL)	8.2	5.7	4.6	4.5	6.1	2.8	5.2
Highest WBC Count (10^3 µL)	9.6	6.4	8.1	10	10.2	3.4	5.2
Lowest Neutrophils (10^3 µL)	5.5	4.3	2.8	2.7	3.6	1.1	3.8
Lowest Lymphocytes (10^3 µL)	3.3	1.1	0.9	0.6	1.5	0.8	18.4

Highest AST (units/L)	12	12	46	29	22	45	
Highest ALT (units/L)	7	8	40	32	27	46	
Highest D-Dimer (µg/mL)			0.2	4.08	0.25	0.31	
Highest CRP (mg/L)			1.6	9.3	5.8	5.2	9.9
Highest Creatinine (mg/dL)	0.51	0.47	0.66	0.6	0.77	0.51	

595

Pregnant patients with severe Covid-19 disease were non-Hispanic white (n=4), Hispanic race unknown (n=1), and race/ethnicity unknown (n=1).

Abbreviations: AST: aspartate transaminase; ALT: alanine aminotransferase; CXR: Chest X-ray; GA: gestational age; CS: cesarean section; ICU: intensive care unit; RR: respiratory rate; WBC: white blood cells

*Age group (5 year increments) is presented to make it less likely that a patient might be identifiable.

† Pre-pregnancy BMI not available. This value represents BMI at SARS-CoV-2 diagnosis, which was at 14 weeks gestation.

‡ This patient had three emergency department visits for respiratory concerns, one of which prompted this hospitalization.

Table 4. Maternal, Pregnancy, and Neonatal Outcomes for Eight Deliveries Among SARS-CoV-2 Infected Pregnant Patients

Characteristics	Deliveries (N=8)*
Delivery Characteristics	
Gestational age at delivery	38.4 (37.5-39.8)
Preterm Birth	1 (12.5)
Labor	
None	2 (25.0)
Spontaneous†	2 (25.0)
Induced‡	4 (50.0)
Outcome	
Live birth	7 (87.5)
Stillbirth	1 (12.5)
Delivery Route	
Vaginal	5 (62.5)
Cesarean§	3 (37.5)
Complications	
Pregnancy	
Gestational diabetes**	1 (12.5)
Gestational hypertension††	2 (25.0)
Cholestasis	1 (12.5)

Delivery	
Placental abruption	1 (12.5)
Non-reassuring fetal status / fetal distress	3 (37.5)
Postpartum	
Postpartum preeclampsia with severe features‡‡	2 (25.0)
SARS-CoV-2 testing	
Days between positive test and delivery	7.5 (5.0-11.5)

599

* Characteristics summarized as n(%) or median(IQR).

† One patient with spontaneous onset of labor had labor subsequently augmented.

‡ Reasons for inductions included fetal demise n=1, premature rupture of membranes n=1, diabetes n=1, hypertensive disorders of pregnancy n=1, growth restrictions n=1, scheduled induction n=2. No inductions of labor were performed to improve maternal lung function.

§ Cesarean section indications included (multiple indications in some cases): repeat cesarean delivery n=2, non-reassuring fetal status=1, diabetes n=1, respiratory compromise n=1, second stage arrest n=1, malpresentation n=1, Covid-19 n=2 (decision in the context of Covid-19 and other co-morbidities n=1, worsening respiratory status n=1), other n=1 (cholestasis, history of shoulder dystocia, fetal macrosomia this pregnancy)

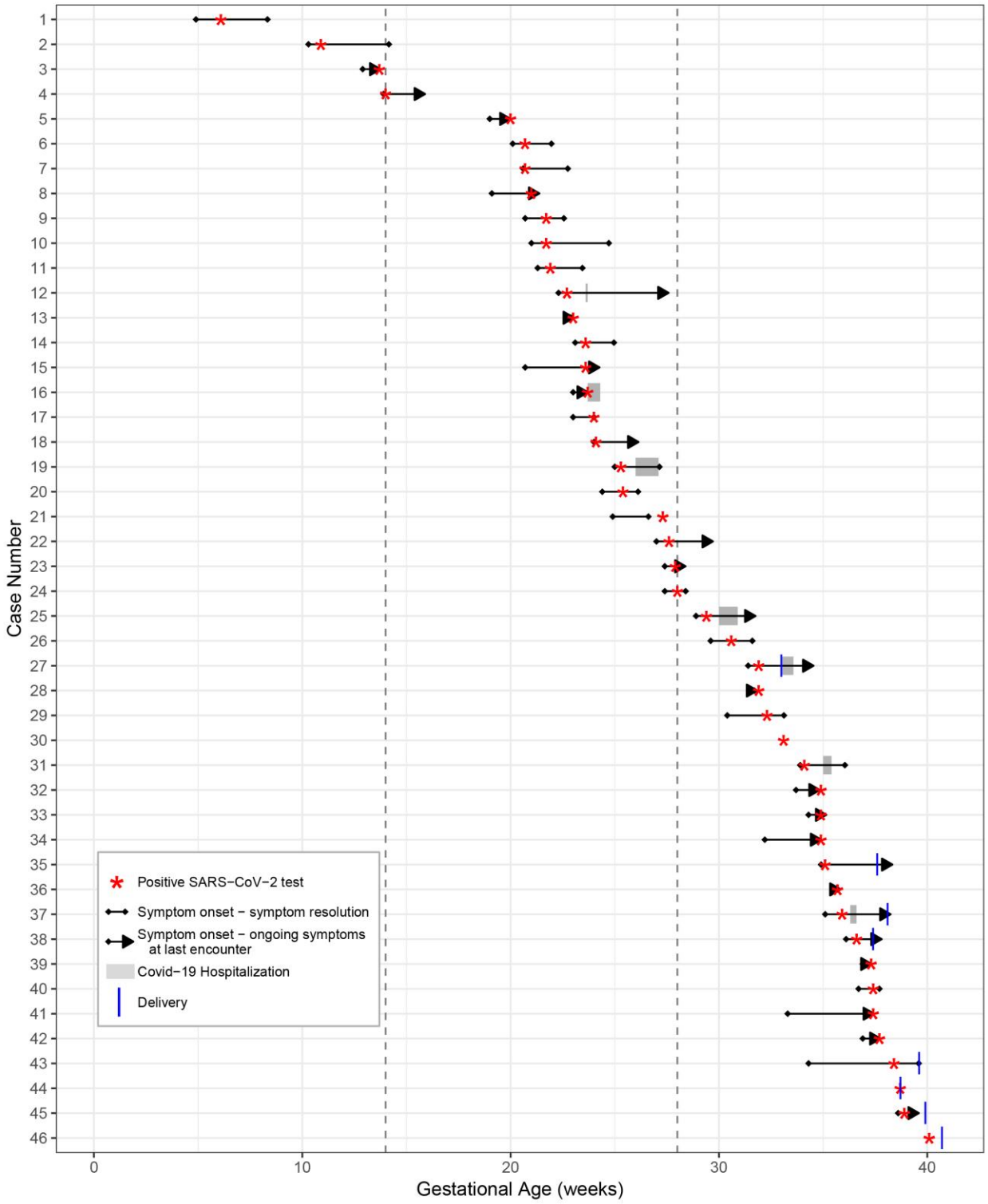
** Treated with insulin.

†† Diagnosed concurrently with (n=1) or after positive SARS-CoV-2 test (n=1)

‡‡ Both cases were defined as severe by blood pressure criteria.

FIGURE LEGENDS

Figure 1. Timeline of Symptom Onset and Resolution, Laboratory Testing, Covid-19 Hospital Admission and Delivery for 46 Pregnant Patients. Time is shown on the x-axis and is measured by gestational age in weeks. Each line of the y-axis reflects an individual patient. Gestational age of first positive SARS-CoV-2 test (red star), length of symptoms (black lines; gestational age at symptom onset marked by black dot, gestational age/days postpartum at symptom resolution marked by black dot if resolved and a black arrow if ongoing at last encounter (censoring), length of Covid-19 hospitalizations (grey bar), and gestational age at delivery (blue vertical line) are shown for each patient, as applicable. Three patients were asymptomatic. Of the seven patients hospitalized for Covid-19 associated respiratory concerns, six were severe (Table 3).


Case Number
Gestational Age (weeks)
0
10
20
30
40
Positive SARS−CoV−2 test
Symptom onset − symptom resolution
Symptom onset − ongoing symptoms at last encounter
Covid−19 Hospitalization
Delivery

611