The Epidemiology of COVID-19 in Pregnancy

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Abstract: As of November, 2021 there have been more than 250 million coronavirus disease-2019 (COVID-19) cases worldwide and more than 5 million deaths. Obstetric patients have been a population of interest given that they may be at risk of more severe infection and adverse pregnancy outcomes. The purpose of this review is to assess current epidemiology and outcomes research related to COVID-19 for the obstetric population. This review covers the epidemiology of COVID-19, symptomatology, transmission, and current knowledge gaps related to outcomes for the obstetric population.
Key words: COVID-19, maternal safety, maternal outcomes, severe maternal morbidity

Introduction

In December 2019, a cluster of severe viral pneumonia cases was identified in Wuhan, China that rapidly spread to become a global pandemic with more than 250 million cases and 5 million

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deaths as of November 2021.[1] Coronavirus disease of 2019, commonly known as COVID-19, is the disease caused by the novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] As of November, 2021, there have been 46 million confirmed cases and 750,000 deaths in the United States according to the World Health Organization.[3] Genomic sequencing of SARS-CoV-2 found that this virus is related to 2 other viruses: severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome-related coronavirus (MERS-CoV).[4,5]

In pregnancy, because of physiological and immunologic changes, there was concern for potential increased respiratory morbidity from viral pathogens similar to that as from SARS-CoV-1 and MERS-CoV.[6] While most people with COVID-19 infection will be asymptomatic or only exhibit mild symptoms, progression to severe acute respiratory syndrome and multiorgan failure may occur with increased risk among those with comorbidities such as diabetes and hypertension.[7]

Obstetric patients have been a population of interest, given concerning data suggesting higher risk for severe infection and negative pregnancy outcomes. This review focuses on COVID-19 epidemiology related to the obstetric population. First, we review United States and global COVID-19 infection rates in the obstetric population. Second, we review the epidemiology of disease severity including estimates of asymptomatic and symptomatic infections and risk for needing intensive care unit (ICU) care. Third, we review risk factors for COVID-19 infection and complications including comorbid medical conditions and social determinants of health. Fourth, we review epidemiological data on maternal, fetal, and neonatal outcomes.

SARS-COV-2 INFECTION RATES IN THE OBSTETRIC POPULATION

Described rates of infection in the obstetric population vary by region, testing period during the pandemic, and testing methodology.

United States

Data available from the Centers for Disease Control and Prevention (CDC) provides the largest sample estimating infection rates among pregnant persons in the United States. A Morbidity and Mortality Weekly Report from January 22 to June 7, 2020 analyzing national infection surveillance data evaluated reports of 326,335 women of reproductive age (15 to 44 y) who had positive test results for SARS-CoV-2. Data on pregnancy status were available for 91,412 (28.0%) with laboratory-confirmed infections; among these, 8207 (9.0%) were pregnant.[3] The percentage of women of reproductive age with positive test results for SARS-CoV-2 was higher than expected given that ~5% of women aged 15 to 44 years are pregnant at any point in time. A potential cause for this difference was more frequent contact with the health care system and increased

frequency of screening. An updated CDC report reviewed cases from January 22 to October 3, 2020 and included 461,825 reproductive age women with positive test results for SARS-CoV-2 with data on pregnancy status and found that 6.6% were pregnant. Among the 461,825 reproductive age women, 409,462 (88.7%) were symptomatic. Among all symptomatic women, 23,434 (5.7%) were reported to be pregnant.[4] These findings broadly suggest that in the US SARS-CoV-2 infection and related symptomatology occurred at similar or higher rates among pregnant women compared with nonpregnant reproductive age women.

US Regional Data: Universal testing: early in the pandemic, a number of hospitals in the United States and internationally performed universal SARS-CoV-2 laboratory screening for obstetric admissions, providing infection rates for local populations. These screening initiatives were put in place in part because of the suspected high rate of asymptomatic carriers of the virus in the general population.[5] There have been a series of publications detailing the results of universal testing protocols (Table 1). New York City was at the epicenter of the first wave of the pandemic in the United States. As such, major medical systems in this area were early adopters of universal testing protocols and reported on their findings. New York City-based cohorts ranged in size from 215 to 675 patients. Rates of 10.4% to 19.9% SARS-CoV-2 positivity were documented in these cohorts with 66% to 100% of positive patients asymptomatic at the time of testing.[6–10] Buckley and colleagues additionally reviewed results of universal testing of asymptomatic support persons for patients admitted in labor in New York City. Of 199 support persons who underwent SARS-CoV-2 testing, the prevalence of infection was found to be 19.6% with 39 support persons having a positive test result for infection.[9]

TABLE 1.   ***Study Findings From Single-center Centers Performing Universal SARS-CoV-2 Screening for Obstetric Hospitalizations***

References	Location	Time Period	Study, n	Positivity, n (%)	Proportion Asymptomatic, n (%)
Sutton et al[6]	New York City	3/22-4/18/20	215	33 (13.7)	29 (87.9)
Prabhu et al[7]	New York City	3/22-4/20/20	675	70 (10.4)	55 (78.6)
Vintzileos et al[8]	New York City	3/30-4/12/20	161	32 (19.9)	21 (66)
Buckley et al[9]	New York City	4/4-4/15/20	307	50 (16.3)	50 (100)
Blitz et al[10]	New York City/ Long Island	4/2- 4/9/ 20	375	64 (17.1)	45 (70.3)
Campbell et al[11]	Southern Connecticut	4/2-4/29/20	770	30 (3.9)	22 (73.3)
Berkowitz et al[12]	Ohio	5/1-5/15/20	492	10 (2.0)	7 (70)
Goldfarb et al[13]	Boston	4/18- 5/5/20	757	20 (2.6)	9 (45)
Fassett et al[14]	California	4/6-5/11/20	3923	17 (0.4)	17 (100)
Yassa et al[15]	Turkey	4/27-5/27/20	296	23 (7.8)	12 (525)
Tanacan et al[16]	Turkey	4/15-6/5/20	206	3 (1.5)	3 (100)
Doria et al[17]	Portugal	3/25-4/15/20	103	12 (11.4)	11 (91.6)
Cardona Perez et al[18]	Mexico	4/22-5/25/20	240	70 (29.0)	60 (86)

The table demonstrates US and international single-center studies evaluating test results for universal SARS-CoV-2 screening for obstetric hospitalizations.

SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2.

Reports on universal testing at other locations within the United States have been published, including Connecticut, Ohio, and California. The published reports describe lower test positive rates with universal testing likely secondary to lower infection rates in the general population during the study period as compared with New York City-based cohorts. Campbell and colleagues presented results of universal testing in patients at three institutions in Southern Connecticut during the spring of 2020. Among asymptomatic patients the SARS-CoV-2 positive rate was 2.9% (22/756).[11] Berkowitz and colleagues described findings from a universal testing cohort through the Cleveland Clinic. There were 10 patients (2%) with positive results, only 3 of whom were symptomatic in a cohort of 492 patients.[12] Goldfarb and colleagues described results from 757 tests collected in Boston over 18 days of universal testing on labor and delivery units. Of those, 139 had symptoms possibly consistent with COVID-19. Of symptomatic women, 11/139 (7.9%) tested positive. Amongst asymptomatic women,

9/618 (1.5%) tested positive. Thus, 9 of 20 patients positive for SARS-CoV-2 at admission (45%) had no symptoms of COVID-19 at presentation.[13] The largest available US-based cohort was published through Kaiser Permanente Southern California. A total of 3923 patients underwent routine SARS-CoV-2 testing on admission to labor and delivery. A total of 17 [0.43%; 95% confidence interval (CI): 0.2%-0.6%] women tested positive, and none of them were symptomatic on admission.[14]

Global

Universal testing protocols were also deployed internationally and several groups outside of the United States have reported on their findings. Two Turkish cohorts have been published. A single institutional study in Istanbul evaluated a total of 296 pregnant patients who underwent screening for SARS-CoV-2 with polymerase chain reaction (PCR) and lung sonography on admission at any gestational age for any indications. This strategy diagnosed 23 pregnant women (7.77%) with SARS-CoV-2 infection. The rates of symptomatic

and asymptomatic patients diagnosed with SARS-CoV-2 were 3.7% (n = 11) and 4.1% (n = 12), respectively. In this study, lung ultrasound was performed to assess its utility in identifying COVID-19 cases. Four of nine women who underwent repeat testing for SARS-CoV-2 upon abnormal lung ultrasound findings were found to be positive (17.4%, n = 4/23).[15] A second prospective cohort study was conducted at a different site in Turkey between April 15, 2020 and June 5, 2020. A total of 206 asymptomatic pregnant women were screened for SARS-CoV-2 positivity upon admission to hospital for delivery. Three of the 206 pregnant women participating in the study had positive RT-PCR tests (1.4%).[16]

Dória et al[17] described a small cohort in northern Portugal of 103 women who underwent universal testing from March 25 to April 15 2020 where a positivity rate of 11.7% was detected with 11 of 12 cases asymptomatic. A cohort from Mexico City found that 29% of patient admitted to labor and delivery were SARS-CoV-2 positive and 86% of positive patients were asymptomatic. Mexico City had a positivity rate of 32% in the general population during the period of study.[18]

Findings from cohorts both in the United States and internationally broadly indicate that while universal SARS-CoV-2 screening may be important in populations with high rates of disease, asymptomatic testing of patients where COVID-19 infections are less common may be of limited utility. When data regarding local SARS-CoV-2 positivity is available in these cohorts, pregnant patients appear to have positive test rates that are similar to general local population at the time of study.

DISEASE SEVERITY

Disease Severity During Pregnancy in Comparison to Nonpregnant Reproductive Age Women

Since the start of the pandemic, there was concern that pregnant persons would be at greater risk of severe morbidity and mortality given attenuated immune response during pregnancy and heightened vulnerability to other respiratory infections such as influenza.[19] While smaller reports, early in the pandemic, did not find pregnant women to be at increased risk of severe disease compared with the general population,[20] subsequent national data has demonstrated some increased risk.[4,21,22]

CDC data has supported increased risk of severe illness among pregnant patients compared with age-matched nonpregnant patients. An initial CDC report indicated that among women with COVID-19, 31.5% of pregnant women were reported to have been hospitalized compared with 5.8% of nonpregnant women. In addition, after adjusting for clinically relevant factors, pregnant women were also significantly more likely to be admitted to the ICU [adjusted risk ratio (aRR): 1.5, 95% confidence interval (CI): 1.2-1.8] and receive mechanical ventilation (aRR: 1.7, 95% CI: 1.2-2.4).[3] An updated CDC report supported these findings and additionally identified an increased risk for needing extracorporeal membrane oxygenation (ECMO) cannulation (0.7 vs. 0.3 per 1000 cases; aRR: 2.4; 95% CI: 1.5-4.0).[4] With regard to specific symptomatic complaints, CDC data has indicated symptomatic pregnant and nonpregnant women with COVID-19 reported similar frequencies of cough (> 50%) and shortness of breath (30%), while pregnant persons less frequently reported headache, muscle aches, fever, chills, and diarrhea.[4] These findings broadly support a modest increased attributable risk among obstetric patients compared with age-matched nonpregnant women.

Several studies have estimated the risk of COVID-19 diagnosis during pregnancy. In an international cohort comparing 706 pregnant patients with COVID-19 diagnoses to 1424 pregnant women without COVID-19 diagnoses, those with COVID-19 carried a 5.04 fold

increased risk of ICU admission, a 22.3 fold relative risk (RR) of maternal mortality, as well as increased RR of preeclampsia (RR: 1.76), preterm birth (RR: 1.34), and severe neonatal morbidity (RR: 2.66). Of note, even asymptomatic COVID-19 patients carried an increased risk of maternal morbidity (RR: 1.24).[23] A large US-based retrospective cohort study included 869,079 pregnant patients who received care at one of 499 academic centers. A total of 2.2% of the cohort had COVID-19. Patients with COVID-19 were significantly more likely to experience preterm birth at rates of 16.4% versus 11.5% ($P < 0.001$). They had significantly higher rates of ICU admission with an odds ratio (OR) of 5.84 ($P < 0.001$), and a 14.33 OR of respiratory intubation and mechanical ventilation ($P < 0.001$), as well as a 10-fold increase in the risk of in-hospital mortality with 0.1% of pregnant patients with COVID-19 dying during admission ($P < 0.01$).[24]

Delta Variant

The Delta variant (B 1.6.17.2) became the dominant strain of Sars-Cov-2 in the United States during the summer of 2021.[2] Data suggest that the Delta variant may be associated with more severe disease in the general population with an increase in transmissibility and vaccine-breakthrough infections.[25,26] There are several preliminary studies which have indicated increased disease transmission and severity associated with Delta infection during pregnancy.

A cohort study from the University of Alabama comparing pre-Delta to Delta COVID-19 infections found Delta increased the need for respiratory support, intubation, and pharmacologic treatment significantly.[27] Similar findings were reported at an additional single-site cohort in Texas. When comparing the pre-Delta time period to the period when Delta variant predominated locally, both the case volume and the proportion of severe or critical illnesses increased significantly ($P < 0.001$) with more than 25% of pregnant patients who were diagnosed between August 29, 2021 and September 4, 2021 requiring admission for severe or critical illness.[28] A third single-site study in Texas found significant increases in rates of symptomatic infection and need for supplemental oxygen support with COVID-19 during the Delta variant dominant period as compared with pre-Delta. In addition, patients were diagnosed at an earlier mean gestational age in the setting of Delta.[29]

Asymptomatic Carrier Rates

In the general population, a majority of SARS-CoV-2 positive patients will be asymptomatic. Asymptomatic carriers have the capacity to infect others, thus propagating COVID-19 spread.[5] Reports available from universal testing data have consistently indicated that in the obstetric population, the majority of patients are asymptomatic.[30,31] Reported rates of that SARS-CoV-2 positivity amongst asymptomatic labor and delivery patient admissions range from 0.45% to 19.9%.[8,14] Amongst patients positive for SARS-CoV-2 on PCR testing in universal testing cohorts, 45% to 100% were described as asymptomatic, with most studies reporting a rate of 66% or greater asymptomatic status.[6,13] Positive testing may indicate an asymptomatic carrier or a "presymptomatic" patient who will later develop clinical symptoms. Sutton et al[6] described that 10% of their cohort who were asymptomatic at the time of testing ultimately developed fever consistent with COVID-19 infection during admission. Other reports of universal testing did not appreciate conversion to symptomatic COVID-19 infection.[11,14] Some evidence from the general population has indicated that clinically recovered patients with continued postviral shedding may be represented in universal screening cohorts, however, data specific to the pregnant population in this scenario are not yet available.[32]

Rates of Disease Severity

Several studies characterized the frequency of different levels of disease severity in pregnant patients with confirmed symptomatic COVID-19 infection. Available data indicate that the majority of patients experience mild disease.

Metz and colleagues studied an observational cohort of patients with SARS-CoV-2 positive testing during a period of universal testing during spring 2020 across 33 US hospitals within the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Of 1219 patients, 579 (47%) were asymptomatic, 326 (27%) had mild illness, 173 (14%) had moderate illness, 98 (8%) had severe illness, and 43 (4%) had critical illness.[30]

Smaller single institution studies have indicated similar findings. An early Chinese study reviewed 118 women who carried a symptomatic COVID-19 diagnosis and were admitted to the hospital for obstetric or infectious indications. In this group (92%) had mild disease, and 9 (8%) had severe disease (hypoxemia), 1 of whom received noninvasive mechanical ventilation (critical disease). Severe disease developed in 6 of the 9 women after delivery, and the woman who received noninvasive mechanical ventilation did so after delivery.[20] Breslin and colleagues provided early data on the frequency of levels of disease severity in a cohort of women who underwent universal testing on labor and delivery admission in New York City in the spring of 2020. This cohort included 43 patients with positive Sars-CoV-2 testing presenting to an affiliated pair of New York City hospitals from March 13 to March 27, 2020. On the basis of COVID-19 disease severity classification by Wu and McGoogan, 37 women (86%) exhibited mild disease, 4 (9.3%) severe disease, and 2 (4.7%) critical disease; these percentages are similar to those described in nonpregnant adults with COVID-19 (with ~80% developing mild, 15% severe, and 5% critical disease).[33,34] Khoury and colleagues described disease severity based on World Health Organization criteria at a different New York City-based cohort across multiple medical systems. Within this cohort (241 women), 38.6% of women were symptomatic. In symptomatic patients, 26.5% of women met criteria for mild COVID-19, 26.1% for severe, and 5% for critical disease. Admission to the ICU was reported for 17 women (7.1%), and 9 (3.7%) required intubation and mechanical ventilation during their delivery hospitalization.[35]

ICU Admission

National-level data sets have indicated increased risks of ICU admission and invasive ventilation for pregnant women versus nonpregnant reproductive aged women. In the United States, a CDC report found that in addition to hospital admission, pregnant women more frequently require ICU admission (10.5 vs. 3.9 per 1000 cases; aRR: 3.0; 95% CI: 2.6-3.4), invasive ventilation (2.9 vs. 1.1 per 1000 cases; aRR: 2.9; 95% CI: 2.2-3.8) and ECMO (0.7 vs. 0.3 per 1000 cases; aRR: 2.4; 95% CI: 1.5-4.0) compared with nonpregnant reproductive age women patients.[4]

These findings align with national data from Sweden. Collin and colleagues reviewed all pregnant or recently postpartum women admitted to ICU-level care for COVID-19 in Sweden between March 19 and April 20, 2020. Overall, 53 women aged 20 to 45 years were described, with 13 patients either pregnant or recently postpartum. Being admitted to the ICU was more common among pregnant and postpartum women with COVID-19 in Sweden than in nonpregnant women of similar age. The incidence of ICU level of care for COVID-19 infection was 14.4 per 100,000 for pregnant or postpartum women compared with 2.5 per 100,000 for nonpregnant women in the same age group (RR: 5.39,

95% CI: 2.89-10.08). The incidence of requiring invasive mechanical ventilation was also increased in this population with 7.4 per 100,000 pregnant versus 1.8 per 100,000 nonpregnant patients requiring invasive ventilatory support, respectively (RR: 3.48, 95% CI: 1.86-6.52).[22] A prospective national population-based cohort study in the UK was performed using the UK Obstetric Surveillance System (UKOSS) to characterize symptomatic COVID-19 pregnant patients. The cohort included 427 women requiring hospitalization. The estimated incidence of hospital admission with confirmed SARS-CoV-2 infection in pregnancy was 4.9 per 1000 cases. Of these, 41 (10%) women admitted to hospital needed respiratory support and 5 (1%) women died.[21]

SOCIAL AND DEMOGRAPHIC RISK FACTORS

The COVID-19 epidemic has disproportionately affected patients and communities vulnerable both because of medical factors, as well as social determinants of health.[36–38] Data available from obstetric populations reveals that both social determinants of health and underlying medical factors are associated with disease transmission and severity.

Racial and Ethnic Disparities

CDC data indicated racial and ethnic disparities in both incidence and severity of COVID-19 among pregnant patients. Pregnant COVID-19 patients were more frequently identified as Hispanic (29.7%) and less frequently as non-Hispanic White (23.5%) compared with nonpregnant women with a COVID-19 diagnosis (22.6% Hispanic and 31.7% White). Further, while non-Hispanic Black women made up 14.1% of women included in this analysis, they represented 176 (36.6%) of deaths overall, including 9 of 34 (26.5%) deaths among pregnant women and 167 of 447 (37.4%) deaths among nonpregnant women.[4] Other reports have also supported the finding of health disparities by patient race and ethnicity. Blitz and colleagues performed a retrospective study including all pregnant women who were tested for SARS-CoV-2 (both symptomatic and asymptomatic) at 7 hospitals in New York State from April to June 2020 in both urban and suburban settings. PCR test results were obtained for 4674 patients and 11% were ultimately positive. Hispanic and non-Hispanic Black pregnant women were disproportionately affected by SARS-CoV-2. Despite constituting approximately one-third of the study population, they accounted for nearly half of all the cases.[39] Additional studies have found that pregnant patients with SARS-CoV-2 positive test results were younger and were more likely to have public insurance, to identify as Black or Latina, to have preexisting pulmonary disease, and to have living children.[40] Emeruwa and colleagues performed a cross-sectional cohort study of 100 women who tested positive for SARS-CoV-2 infection among 673 gravid patients (14.9%) who delivered during the spring of 2020. There was a significantly higher SARS-CoV-2 infection rate among Hispanic women compared with non-Hispanic White women (18.1% vs. 9.4%, $P \leq 0.01$). However, in this group, positivity rates of non-Hispanic Black women (12.7%) were not significantly different from non-Hispanic White women.[41]

Built Environment

Emeruwa and colleagues examined the association of the built environment with SARS-CoV-2 acquisition in a cross-sectional study of 434 pregnant patients in New York City who underwent universal SARS-CoV-2 PCR testing in the spring of 2020. This study evaluated characteristics of the built environment and socioeconomic status. They found that SARS-CoV-2 positivity was associated with neighborhood and building-level markers of large household membership, household crowding, and low socioeconomic status.[42]

Other Social Determinants of Health

Prasannan and colleagues evaluated characteristics of patients from a different New York based medical system from April through June 2020 in a cross-sectional cohort sample. 4873 patients were included who underwent universal SARS-CoV-2 PCR testing. Patients in this cohort were noted to have increased risk of SARS-CoV-2 positivity if they had public health insurance, limited English proficiency, and resided in low-income neighborhoods with less educational attainment based on evaluation of residential zip codes.[43] Sakowicz et al[40] identified public insurance as a risk factor for SARS-CoV-2 acquisition, as well as unmarried status.

In sum, these findings support that in addition to racial disparities more crowded housing, low income, and employment requiring interactions outside of the home contribute to risk of SARS-CoV-2 infection in disadvantaged populations.

Medical risk factors: medical factors contribute both to SARS-CoV-2 acquisition and COVID-19 severity in both the general and obstetric population.

Maternal Age

For both pregnant and nonpregnant women, CDC data demonstrated that ICU admissions, receipt of invasive ventilation and death were more common among women aged 35 to 44 years than among those aged 15 to 24 years.[4] This finding was supported in a meta-analysis by Allotey et al that demonstrated advanced maternal age was a risk factor for severe COVID-19 by WHO criteria (aOR: 1.78, 95% CI: 1.25-2.55; $I^2 = 9\%$; 4 studies; 1058 women).[44]

Gestational Age

In several studies, the majority of pregnant patients hospitalized for COVID-19 infection were in the late second or third trimester.[20,35,45–47] However, it is unclear if this indicates increased risk of acquisition in later pregnancy or a higher

likelihood of patients undergoing SARS-CoV-2 testing upon presentation with obstetric complaints.

Parity

Increased parity, which is often associated with advancing age and may imply larger household size, has been identified as a risk factor for SARS-CoV-2 acquisition in several studies.[40,44]

Obesity

Multiple reports have indicated that elevated body mass index carries a risk of contracting COVID-19 both in pregnancy and in the general population.[35,44,48] In addition, high body mass index was found to increase risk of severe COVID-19 infection with an adjusted OR of 2.4 in the largest available meta-analysis.[44]

Comorbidities

Common medical comorbidities have been associated with increased risk of COVID-19 diagnosis and severity both in pregnant and nonpregnant populations. Metz et al found that pre-existing medical comorbidities including asthma, pregestational diabetes, chronic cardiovascular disease, and seizure disorders were associated with a significantly increased risk of severe disease.[30] Pre-existing maternal comorbidity is a risk factor for admission to an ICU and invasive ventilation among obstetric patients based on meta-analysis data with aORs of 4.2 and 4.5, respectively.[44] Prasannan et al[43] determined that pre-existing pulmonary disease is also a risk factor for disease acquisition. A systematic review by Allotey et al[44] assessed characteristics of pregnant women with confirmed symptomatic cases of COVID-19 and found chronic hypertension and pre-existing diabetes were associated with severe COVID-19 in pregnancy. In a retrospective cohort examining pregnant women hospitalized with severe or critical COVID-19 infection, 25% had a pulmonary

condition and 17% had cardiac disease.[45] Chronic lung disease, diabetes mellitus, and cardiovascular disease were more commonly reported among pregnant women than among nonpregnant women diagnosed with COVID-19 in the most updated CDC analysis.[4]

MATERNAL OUTCOMES

Maternal Mortality

Initial CDC data indicated that while pregnant patients were more likely to require ICU admission or mechanical ventilation than their age-matched nonpregnant peers, their risk of death was not significantly different. Sixteen (0.2%) COVID-19-related deaths were reported among pregnant women aged 15 to 44 years, and 208 (0.2%) such deaths were reported among nonpregnant women (aRR: 0.9, 95% CI: 0.5-1.5).[3] However, an updated CDC report extending through October 2020 found that in addition to pregnant women more frequently requiring ICU admission there was a 70% increased risk of death in pregnant versus nonpregnant women with COVID-19 (aRR: 1.7, 95% CI: 1.2-2.4).[4]

Mode of Delivery

Several studies have indicated higher rates of cesarean birth in patients with COVID-19. A systematic review including 39 studies found that between 52.3% and 95.8% of COVID patients underwent cesarean birth.[49] Prabhu et al[7] observed increased cesarean birth rates even in asymptomatic COVID positive patients compared with noninfected patients, with rates of ~40% versus 30%, respectively. Metz et al[30] found that severe COVID-19 infection was associated with increased risk of cesarean birth (59.6% vs. 34.0%, aRR: 1.57, 95% CI: 1.30-1.90).

Other Maternal Outcomes

Metz and colleagues found that in adjusted analyses, severe COVID-19 was associated with increased risk for postpartum hemorrhage (aRR: 2.02, 95% CI: 1.18-3.45), hypertensive disorders of pregnancy (aRR: 1.61, 95% CI: 1.18-2.20), and preterm birth (aRR: 3.53, 95% CI: 2.42-5.14) compared with asymptomatic COVID-19. This cohort also identified a 6% rate of venous thromboembolism in those patients with severe disease.[30]

Fetal and Neonatal Outcomes

Pregnancy outcome data is available from the CDC through October 2020. Among 4527 fetuses and infants, the outcomes comprised 4495 (99.3%) live births (including 79 sets of twins and one set of triplets), 12 (0.3%) pregnancy losses at below 20 weeks' gestation, and 20 (0.4%) losses at 20 weeks' gestation or above. Among 3912 infants with reported gestational age, 506 (12.9%) were preterm, including 149 (3.8%) at below 34 weeks and 357 (9.1%) at 34 to 37 weeks. Frequency of preterm birth did not differ by maternal symptom status ($P = 0.62$) including among women hospitalized at the time of infection ($P = 0.81$).[11] Nine (0.2%) in-hospital neonatal deaths were reported. Among term infants (37 wk gestation or above), 9.3% were admitted to an ICU (ICU); however, reason for admission was often missing. Information on infant SARS-CoV-2 testing was reported from 13 jurisdictions; among 923 infants with information, 313 (33.9%) were not tested.[47]

Vertical Transmission

Vertical transmission rates have been low in maternal-neonates dyads studied to date, ranging from 0 to 5% in smaller cohorts.[7,8,21,50–52] In a review performed by Kyle et al[53] of 836 total newborns studied, 35 newborns (4.2%) tested positive through PCR. In the most recent CDC cohort, among 610 (21.3%) infants for whom molecular test results were reported, 16 (2.6%) results were positive. The percent positivity was 4.3% (14 of

328) among infants born to women with documentation of infection identified ≤ 14 days before delivery and 0% (0 of 84) among those born to women with documentation of infection identified > 14 days before delivery.[47]

Those neonates who have had documented cases of vertical transmission have thus far demonstrated favorable neonatal outcomes. With the majority of neonates with asymptomatic infections, and of those with clinical findings, the majority present as mild respiratory symptoms with a recovery to baseline respiratory status within 2 weeks.[53]

Preterm Birth

The greatest source of potential morbidity and mortality to neonates of COVID-infected mothers to date appears to be an increased rate of preterm birth, particularly iatrogenic preterm birth in the setting of severe maternal infection.[45] Reported rates of preterm birth have been estimated at ~22% in a recent systematic review, although the data may over-represent patients managed for severe or critical disease severity.[53] In the most recent CDC cohort, among 3,912 infants with reported gestational age, 506 (12.9%) were preterm, including 149 (3.8%) at below 34 weeks and 357 (9.1%) at 34 to 37 weeks. Frequency of preterm birth did not differ by maternal symptom status ($P = 0.62$).[47] In the NICHD MFMU cohort, severe-critical maternal illness was associated with NICU admission and lower birth weight. Preterm births in this group were indicated (rather than spontaneous) in 83% of cases.[30]

Other Outcomes

Available data have not indicated an increase in low Apgar scores at delivery, small for gestational age babies or birth defects in the setting of COVID-19 as compared with population baselines.[47,53] However, fetal and neonatal outcomes data available to date largely reflect outcomes associated with infections in the late second and third trimesters, thus further research is needed to characterize neonatal impact of maternal infection at earlier gestational ages. However, the limited data available thus far have not detected significant increases in other poor fetal and neonatal outcomes. In addition, available data from case-control and retrospective cohort studies has not identified an increased risk of spontaneous abortion related to maternal COVID-19 infection.[50,54]

Discussion

As the COVID-19 global pandemic continues to evolve, there are a variety of epidemiologic studies offering insight into the impact of COVID-19 on the obstetric population. From these cohort studies, it appears that pregnant patients test positive for SARS-Cov-2 at least as frequently as age-matched nonpregnant controls.[4] Social determinants of health have been demonstrated to increase the risk of COVID-19 transmission, including non-Hispanic Black and Hispanic ethnicity, lower socioeconomic class, and larger household size.[40–43] Medical factors, including increasing maternal age, obesity, and pre-existing medical comorbidities such as chronic hypertension, diabetes, and asthma, have shown an association with increased risk of severe disease.[30] Pregnant patients are at some increased risk of increased disease severity, including ICU admission and invasive ventilation, including ECMO, compared with age-matched nonpregnant patients. In addition, recent CDC data have indicated increased risk of COVID-19 associated death compared with age-matched controls.[4,21,22] While symptomatic COVID-19 infection is associated with increased risk of iatrogenic preterm birth and its sequelae, available data indicated that vertical transmission rates are low and neonates have not demonstrated severe infections.[30,47]

References

1. World Health Organizaiton. WHO Coronavirus (COVID-19 Dashboard). Available at: https://covid19.who.int/. Accessed July 14, 2021.
2. Centers for Disease Control and Prevention. COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed May 12, 2021.
3. Ellington S, Strid P, Tong VT, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status-United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:769–775.
4. Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status-United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1641–1647.
5. Wilmes P, Zimmer J, Schulz J, et al. SARS-CoV-2 transmission risk from asymptomatic carriers: results from a mass screening programme in Luxembourg. *Lancet Reg Health Eur*. 2021;4: 100056.
6. Sutton D, Fuchs K, D'Alton M, et al. Universal screening for SARS-CoV-2 in women admitted for delivery. *N Engl J Med*. 2020;382:2163–2164.
7. Prabhu M, Cagino K, Matthews KC, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. *BJOG*. 2020;127:1548–1556.
8. Vintzileos WS, Muscat J, Hoffmann E, et al. Screening all pregnant women admitted to labor and delivery for the virus responsible for coronavirus disease 2019. *Am J Obstet Gynecol*. 2020;223: 284–286.
9. Buckley A, Bianco A, Stone J. Universal testing of patients and their support persons for severe acute respiratory syndrome coronavirus 2 when presenting for admission to labor and delivery at Mount Sinai Health System. *Am J Obstet Gynecol MFM*. 2020;2:100147.
10. Blitz MJ, Rochelson B, Rausch AC, et al. Universal testing for coronavirus disease 2019 in pregnant women admitted for delivery: prevalence of peripartum infection and rate of asymptomatic carriers at four New York hospitals within an integrated healthcare system. *Am J Obstet Gynecol MFM*. 2020;2:100169.
11. Campbell KH, Tornatore JM, Lawrence KE, et al. Prevalence of SARS-CoV-2 among patients admitted for childbirth in Southern Connecticut. *JAMA*. 2020;323:2520–2522.
12. Berkowitz KM, Goje O, Eaton J. Implementation of universal testing for severe acute respiratory syndrome coronavirus 2 in pregnant women with intended admission for delivery. *Am J Obstet Gynecol*. 2020;223:782–783.
13. Goldfarb IT, Diouf K, Barth WH, et al. Universal SARS-CoV-2 testing on admission to the labor and delivery unit: low prevalence among asymptomatic obstetric patients. *Infect Control Hosp Epidemiol*. 2020;41:1095–1096.
14. Fassett MJ, Lurvey LD, Yasumura L, et al. Universal SARS-Cov-2 screening in women admitted for delivery in a large managed care organization. *Am J Perinatol*. 2020;37:1110–1114.
15. Yassa M, Yirmibes C, Cavusoglu G, et al. Outcomes of universal SARS-CoV-2 testing program in pregnant women admitted to hospital and the adjuvant role of lung ultrasound in screening: a prospective cohort study. *J Matern Fetal Neonatal Med*. 2020;33:3820–3826.
16. Tanacan A, Erol SA, Turgay B, et al. The rate of SARS-CoV-2 positivity in asymptomatic pregnant women admitted to hospital for delivery: experience of a pandemic center in Turkey. *Eur J Obstet Gynecol Reprod Biol*. 2020;253:31–34.
17. Dória M, Peixinho C, Laranjo M, et al. Covid-19 during pregnancy: a case series from an universally tested population from the north of Portugal. *Eur J Obstet Gynecol Reprod Biol*. 2020;250: 261–262.
18. Cardona-Pérez JA, Villegas-Mota I, Helguera-Repetto AC, et al. Prevalence, clinical features, and outcomes of SARS-CoV-2 infection in pregnant women with or without mild/moderate symptoms: results from universal screening in a tertiary care center in Mexico City, Mexico. *PLoS One*. 2021;16:e0249584.
19. Sappenfield E, Jamieson DJ, Kourtis AP. Pregnancy and susceptibility to infectious diseases. *Infect Dis Obstet Gynecol*. 2013;2013:752852.
20. Chen L, Li Q, Zheng D, et al. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. *N Engl J Med*. 2020;382:e100.
21. Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ*. 2020;369:m2107.
22. Collin J, Byström E, Carnahan A, et al. Public Health Agency of Sweden's Brief Report: pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. *Acta Obstet Gynecol Scand*. 2020;99:819–22.
23. Villar J, Ariff S, Gunier RB, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The INTERCOVID Multinational Cohort Study. *JAMA Pediatr*. 2021;175:817–826.
24. Chinn J, Sedighim S, Kirby KA, et al. Characteristics and outcomes of women with COVID-19

giving birth at US Academic Centers During the COVID-19 Pandemic. *JAMA Netw Open*. 2021;4: e2120456–e2120456.

25. Fisman DN, Tuite AR. Progressive increase in virulence of novel SARS-CoV-2 variants in Ontario, Canada. *bioRxiv*. 2021. [Epub ahead of print].

26. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med*. 2021;385: 585–594.

27. Seasely AR, Blanchard CT, Arora N, et al. Maternal and perinatal outcomes associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta (B.1.617.2) Variant. *Obstet Gynecol*. 2021. [Epub ahead of print].

28. Adhikari EH, SoRelle JA, McIntire DD, et al. Increasing severity of COVID-19 in pregnancy with Delta (B.1.617.2) variant surge. *Am J Obstet Gynecol*. 2021. [Epub ahead of print].

29. Wang AM, Berry M, Moutos CP, et al. Association of the Delta (B.1.617.2) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with pregnancy outcomes. *Obstet Gynecol*. 2021. [Epub ahead of print].

30. Metz TD, Clifton RG, Hughes BL, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). *Obstet Gynecol*. 2021;137:571–580.

31. Khalil A, Hill R, Ladhani S, et al. Severe acute respiratory syndrome coronavirus 2 in pregnancy: symptomatic pregnant women are only the tip of the iceberg. *Am J Obstet Gynecol*. 2020;223: 296–297.

32. Ren X, Ren X, Lou J, et al. A systematic review and meta-analysis of discharged COVID-19 patients retesting positive for RT-PCR. *EClinicalMedicine*. 2021;34:100839.

33. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 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;2:100118.

34. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323: 1239–1242.

35. Khoury R, Bernstein PS, Debolt C, et al. Characteristics and outcomes of 241 births to women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at Five New York City Medical Centers. *Obstet Gynecol*. 2020;136: 273–282.

36. Wang Z, Tang K. Combating COVID-19: health equity matters. *Nat Med*. 2020;26:458.

37. Devakumar D, Shannon G, Bhopal SS, et al. Racism and discrimination in COVID-19 responses. *Lancet*. 2020;395:1194.

38. Maroko AR, Nash D, Pavilonis BT. COVID-19 and inequity: a comparative spatial analysis of New York City and Chicago Hot Spots. *J Urban Health*. 2020;97:461–470.

39. Blitz MJ, Rochelson B, Prasannan L, et al. Racial and ethnic disparity and spatiotemporal trends in severe acute respiratory syndrome coronavirus 2 prevalence on obstetrical units in New York. *Am J Obstet Gynecol MFM*. 2020;2:100212.

40. Sakowicz A, Ayala AE, Ukeje CC, et al. Risk factors for severe acute respiratory syndrome coronavirus 2 infection in pregnant women. *Am J Obstet Gynecol MFM*. 2020;2:100198.

41. Emeruwa UN, Spiegelman J, Ona S, et al. Influence of race and ethnicity on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rates and clinical outcomes in pregnancy. *Obstet Gynecol*. 2020;136:1040–1043.

42. Emeruwa UN, Ona S, Shaman JL, et al. Associations between built environment, neighborhood socioeconomic status, and SARS-CoV-2 infection among pregnant women in New York City. *JAMA*. 2020;324:390–392.

43. Prasannan L, Rochelson B, Shan W, et al. Social determinants of health and coronavirus disease 2019 in pregnancy. *Am J Obstet Gynecol MFM*. 2021;3:100349.

44. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320.

45. Pierce-Williams RAM, Burd J, Felder L, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. *Am J Obstet Gynecol MFM*. 2020;2:100134.

46. Karimi L, Makvandi S, Vahedian-Azimi A, et al. Effect of COVID-19 on mortality of pregnant and postpartum women: a systematic review and meta-analysis. *J Pregnancy*. 2021;2021:8870129.

47. Woodworth KR, Olsen EO, Neelam V, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy—SET-NET, 16 Jurisdictions, March 29-October 14, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1635–1640.

48. Savasi VM, Parisi F, Patanè L, et al. Clinical findings and disease severity in hospitalized pregnant women with coronavirus disease 2019 (COVID-19). *Obstet Gynecol*. 2020;136:252–258.

49. Papapanou M, Papaioannou M, Petta A, et al. Maternal and neonatal characteristics and outcomes of COVID-19 in pregnancy: an overview of systematic reviews. *Int J Environ Res Public Health*. 2021;18. [Epub ahead of print].

50. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. *Am J Obstet Gynecol.* 2020;223:111.e1–111.e14.

51. Ferrazzi E, Frigerio L, Savasi V, et al. Vaginal delivery in SARS-CoV-2-infected pregnant women in Northern Italy: a retrospective analysis. *BJOG.* 2020;127:1116–1121.

52. Dumitriu D, Emeruwa UN, Hanft E, et al. Outcomes of neonates born to mothers with severe acute respiratory syndrome coronavirus 2 infection at a Large Medical Center in New York City. *JAMA Pediatr.* 2021;175:157–167.

53. Kyle MH, Glassman ME, Khan A, et al. A review of newborn outcomes during the COVID-19 pandemic. *Semin Perinatol.* 2020;44:151286.

54. Cosma S, Carosso AR, Cusato J, et al. Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients. *Am J Obstet Gynecol.* 2021; 224:391.e1–391.e7.