

SARS-CoV-2 infection during pregnancy and associated perinatal health outcomes: a national US cohort study

Annette K. Regan, PhD;^{1,2,3} Onyebuchi Arah, MD;^{2,3,4} Deshayne B. Fell, PhD;^{5,6,7} Sheena G. Sullivan, PhD^{2,8,9}

¹ School of Nursing and Health Professions, University of San Francisco, Orange CA, United States

² Fielding School of Public Health, UCLA, Los Angeles CA, United States

³ OptumLabs Visiting Fellow, Prairie MN, United States

⁴ Department of Statistics, College of Letters and Science, UCLLA, Los Angeles CA, United States

⁵ Department of Public Health, Aarhus University, Aarhus, Denmark

⁶ School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

⁷ Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada

⁸ WHO Collaborating Centre for Reference and Research on Influenza, Royal Melbourne Hospital, Melbourne VIC, Australia

⁹ Department of Infectious Diseases, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne VIC, Australia

Corresponding author:

Annette Regan
Assistant Professor
School of Nursing and Public Health
University of San Francisco
480 S Batavia Street
Orange CA 98484
T: +1 714.221.6213
akregan@usfca.edu

Alternate corresponding author:

Sheena Sullivan
Senior Epidemiologist
790 Elizabeth Street
Melbourne VIC 3000, Australia
sheena.sullivan@influenzacentre.org

Abstract Manuscript

Summary: Based a national claims-based cohort study of 78,283 pregnancies, prenatal SARS-CoV-2 infection was associated with increased risk of preterm birth, fetal growth restriction, and delivery complications. Prevention of infection through immunization and other preventive measures could have fetal health benefits.

Abstract

Background: SARS-CoV-2 infection has been associated with increased risk of adverse perinatal health outcomes. However, few large-scale, community-based epidemiological studies have been conducted.

Methods: We conducted a national cohort study using de-identified administrative claims data for 78,283 pregnancies with estimated conception before 30 April 2020 and pregnancy end after 11 March 2020. We identified maternal infections using diagnostic and laboratory testing data. We compared the risk of pregnancy outcomes using Cox proportional hazard models treating COVID-19 as a time-varying exposure and adjusting for baseline covariates.

Results: 2,655 (3.4%) pregnancies had a documented SARS-CoV-2 infection; 3.4% required admission to intensive care, invasive mechanical ventilation or ECMO treatment. COVID-19 during pregnancy was not associated with risk of miscarriage, antepartum hemorrhage, or stillbirth, but was associated with 2-3 fold higher risk of induced abortion (adjusted hazard ratio [aHR] 2.60, 95% CI 1.17-5.78), c-section (aHR 1.99, 95% CI 1.71-2.31), clinician-initiated preterm birth (2.88; 95% CI 1.93, 4.30), spontaneous preterm birth (aHR 1.79, 95% CI 1.37-2.34), fetal growth restriction (aHR 2.04, 95% CI 1.72-2.43), and postpartum hemorrhage (aHR 2.03, 95% CI 1.6-2.63).

Conclusions: Prenatal SARS-CoV-2 infection was associated with increased risk of adverse pregnancy outcomes. Prevention could have fetal health benefits.

Key words: SARS-CoV-2; COVID-19; pregnancy outcomes; epidemiology

Background

COVID-19, the disease caused by the SARS-CoV-2 virus, can result in serious, potentially life-threatening respiratory disease. Several conditions place certain adults at higher risk of severe COVID-19, including immunocompromising conditions, diabetes, heart disease, liver disease, and other. More recently, the Centers for Disease Control and Prevention (CDC) listed pregnancy as a medical condition placing adults at higher risk of severe infection. Emerging surveillance data have shown that pregnant individuals may be at increased risk of a severe outcome following maternal SARS-CoV-2 infection [1, 2]. Early data from Wuhan, China suggested no increased risk of severe outcomes for pregnant individuals [3]; however, more recent and robust evidence from a living systematic review and large case series from the US has shown that pregnant individuals are at higher risk of hospitalization, intensive care unit (ICU) admission and death from COVID-19 compared to non-pregnant adults of reproductive age [4, 5].

A living systematic review of 192 studies last updated on March 2021 [6] concluded that compared to their uninfected counterparts, pregnant individuals infected with SARS-CoV-2 have higher mortality and a higher risk of ICU admission [4]. Moreover, their pregnancies are more likely to be preterm and end in stillbirth [4]. These risks have also been reported in a large claims-based study of over 400,000 pregnancies in the US [5] and a pooled Nordic study of over 300,000 pregnancies [7]. Other factors that have been variously reported to increase the risks of severe outcomes or occur more frequently in pregnant individuals infected with SARS-CoV-2, include myocardial infarction, eclampsia, pre-eclampsia, and gestational diabetes [5]. Evidence of vertical transmission of SARS-CoV-2 has been reported [8], but neonatal infection has more commonly been associated with post-delivery infection [8, 9].

Despite the large number of studies, there remain major gaps in our knowledge of how SARS-CoV-2 impacts pregnancy health. First, although a large number of studies have been published since the beginning of the COVID-19 pandemic, these have been mostly small, regional, hospital-based studies [4]. Second, the majority of studies to date have focused on hospitalized patients, often identified at

the time of delivery, which will over-represent more severe SARS-CoV-2 infections and may be driven by routine testing at admission for delivery. Second, all observational studies which have examined pregnancy outcomes among all pregnancies presenting run the risk of right truncation bias or live-birth bias, if not properly addressed [10, 11]. As a result, these studies might under- or over-estimate the risks of pregnancy outcomes. Finally, many studies have included as risk factors conditions which may be mediating factors for severe disease, which can also lead to spurious estimates.

Here, we report on outcomes associated with both hospitalized and community COVID-19 diagnoses anytime during pregnancy using large administrative claims and electronic health record data from the OptumLabs[®] Data Warehouse (OLDW). We included only pregnancies conceived prior to 30 April 2020 to allow sufficient time for full follow up, thereby averting right truncation.

Methods

We conducted a claims-based cohort study using de-identified administrative claims and electronic health record (EHR) data from the OLDW [12]. The database includes longitudinal health information for enrollees across the United States. Claims data in OLDW include medical and pharmacy claims, laboratory results and enrolment records for commercial enrollees. Pregnancies were identified from facility and physician claims data using a previously validated algorithm (**eTable 1**) [13]. The cohort included individuals with an estimated date of conception before 30 April 2020 (i.e., allowing ≥ 43 weeks of follow up to prevent cohort truncation bias)[10] and pregnancy end date after 11 March 2020 (i.e., declaration of COVID-19 pandemic status). We excluded molar and ectopic pregnancies from our analysis. We extracted physician, facility and laboratory claims records in addition to EHR data for one year preceding and 30 days following the date the pregnancy ended. Pregnancies were included in the final analysis if they were continuously enrolled in the health insurance plan for one year preceding the date of delivery and 30 days after the date of delivery. To evaluate early pregnancy outcomes, including miscarriage and induced abortion, we extracted a sub-cohort with a date of

conception between 1 January and 30 April 2020, which restricted the cohort to pregnancies where exposure to SARS-CoV-2 during first trimester was possible. *Variable measurement*

We identified SARS-CoV-2 cases based on the presence of a COVID-19 diagnosis in a facility or physician claim, their EHR, or a positive laboratory test result for a SARS-CoV-2 laboratory test (**eTable 2**). We classified COVID-19 as “severe” if they had a medical record indicating diagnosis of acute respiratory distress syndrome or use of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) treatment (**eTable 2**). Participants without severe symptoms and with no record of hospital diagnosis coinciding with the COVID-19 admission were classed as having “mild” COVID-19 symptoms.

Information on maternal age, race/ethnicity, residence, educational attainment, and household income were derived from enrollment data and linked data supplied by an external vendor. Socioeconomic variables were obtained from a third-party vendor. In brief, the third-party vendor applies imputation procedures to derive race/ethnicity, education level and household income based on a variety of publicly and privately available data sources. Race/ethnicity is imputed based on a model using an individual’s full name and geographic location. Education level is derived from the US Census Bureau’s American Community Survey. Educational attainment is assigned to the individual based on the median level of education achieved among all residents 25 years and older within a census block group. Household income is imputed based on a model using public and private consumer data (e.g., loan amounts and loan payments, credit card statements). We identified pre-existing health conditions and pregnancy complications using medical claims records (**eTable 3**). Medical claims information was also used to identify pregnancy complications and outcomes (**eTable 1**). Early pregnancy outcomes included miscarriage and induced abortion. Pregnancy complications (including hyperemesis, antepartum hemorrhage, pre-eclampsia, gestational diabetes, pre-labor rupture of membranes, and placental abruption) and birth outcomes (cesarean section, induction of labor, clinician-induced preterm birth, spontaneous preterm birth, fetal growth restriction, and stillbirth) were evaluated for pregnancies with gestational length ≥ 20 weeks.

Statistical analysis

We measured the incidence of SARS-CoV-2 infection among pregnant individuals and estimated proportionate severity of prenatal SARS-CoV-2 infection as the proportion of COVID-19 cases classed as “severe.” We compared incidence rates by sociodemographic and chronic health factors using Poisson regression with robust standard errors to account for limited number of available predictors. We adjusted for the timing of pregnancy by including the week of pregnancy conception as a B-spline (a cubic spline with three knots) in the model. Missing covariate information was imputed using expectation-maximization with bootstrapping procedures in the `amelia()` package in R.[14]

To estimate the risks of adverse pregnancy outcomes among SARS-CoV-2 infected pregnancies compared to uninfected pregnancies, we used Cox proportional hazard models with gestational age (in weeks) as the underlying time variable. Models treated COVID-19 as a time-varying exposure. Adjusted models accounted for maternal age, race/ethnicity, household income, presence of a pre-existing medical condition (yes/no), and week of pregnancy conception (cubic spline). We performed separate models by the trimester of SARS-CoV-2 infection (first, second or third) to estimate the risk of adverse pregnancy outcomes by gestational age at infection.

We performed additional analyses comparing the risks of adverse pregnancy outcomes for severe COVID-19 to mild COVID-19. To evaluate the sensitivity of our findings to potential variation in COVID-19 diagnoses, we performed several sensitivity analyses. First, we restricted to individuals with a positive or negative test result for COVID-19 during pregnancy. Second, since testing may occur routinely at admission for delivery, we stratified our analyses by proximity of the SARS-CoV-2 infection to delivery (within 3 days of delivery or ≥ 3 days). We did not perform any modelling where there were < 11 exposed pregnancies with a pregnancy outcome (consistent with OLDW criteria for reporting results) [12].

Because this study involved analysis of pre-existing, de-identified data, it was considered exempt from Institutional Review Board approval.

Results

Between 11 March 2020 and 31 January 2021, a total of 78,283 pregnancies were identified, of which 2,655 pregnancies (3.4%, 95% CI 3.3-3.5%) had a record SARS-CoV-2 infection (**eFigure 1**); 2,299 (86.6%) had only a COVID-19 diagnosis, 140 (5.3%) had only a positive laboratory test, and 216 (8.1%) had both a positive test and a COVID-19 diagnosis code. Of the 356 cases identified through laboratory testing, 343 tests (96.3%) were conducted by PCR and the remaining 13 were performed using serology; 1,122 of the COVID-19 cases (42.2%, 95% CI 40.4-44.2%) coincided with hospital admission and 91 (3.4%, 95% CI 2.8-4.2%) coincided with admission to intensive care, with documented acute respiratory distress syndrome or invasive mechanical ventilation or ECMO treatment. A total of 27 deaths occurred among individuals in the cohort, equating to a maternal mortality rate of 32 per 100,000 livebirths); 14 deaths occurred at the time of delivery. This was too few to allow comparative analysis.

The median time from infection to delivery or pregnancy end was 28 days (IQR 3-86); 790 infections (29.7%) occurred within 3 days of delivery or pregnancy end. The majority of COVID-19 infections were identified during the third trimester (n=1,971; 74.2%); 513 (19.3%) infections occurred in second trimester and 171 (6.4%) in first trimester. Among those with a conception date between January and April 2020 (n=29,221), 1,679 (5.7%, 95% CI 5.5-6.0%) were diagnosed with COVID-19; 1,080 (64.3%) infections occurred in third trimester, 428 (25.5%) in second and 171 (10.2%) in first trimester (**eFigure 2**). The median gestational age at infection was 34 weeks (IQR 26-37); median gestational age for “mild” and “severe” infections were similar (34 vs. 35 weeks, respectively) (**Figure 1**).

The incidence of SARS-CoV-2 infection declined as maternal age increased (**Table 1**). COVID-19 infection was higher among non-Hispanic Black individuals (RR 1.54, 95% CI 1.43-1.65) and Hispanic individuals (RR 1.73, 95% CI 1.64-1.82) compared to non-Hispanic White individuals. Those with asthma (RR 1.17, 95% CI 1.03-1.31), chronic hypertension (RR 1.20, 95% CI 1.04-1.36), or an immune disorder (RR 2.42, 95% CI 1.90-2.94) were more likely to have a SARS-CoV-2

infection. Proportionate severity of COVID-19 was higher for those with asthma compared to those without (RR 3.12, 95% CI 2.62-3.62). Those who conceived between 1 January and 30 April 2020 were more likely to have a COVID-19 infection but did not have higher proportionate severity (**Table 1**).

A total of 7,366 (9.4%) pregnancies resulted in miscarriage, 1,187 (1.5%) in induced abortion, and 401 (0.5%) in stillbirth. The remaining 69,329 (88.6%) ended in live birth. Among those with a viable pregnancy (i.e., live or stillborn; n=69,730), 3,478 (5.0%) participants were diagnosed with hyperemesis, 8,098 (11.6%) with gestational diabetes, 3,443 (4.9%) with pre-eclampsia, 4,883 (7.0%) with antepartum hemorrhage, and 821 (1.2%) with placental abruption. A total of 8,716 (12.5%) participants experienced premature rupture of membranes, 19,319 (27.7%) had induction of labor, 12,299 (17.6%) had cesarean section, and 3,977 (5.7%) experienced postpartum hemorrhage; 3,754 (5.4%) pregnancies resulted in spontaneous preterm birth, 1,104 (1.6%) were born preterm after clinician initiation, and 8,155 (11.7%) resulted in fetal growth restriction.

In adjusted hazard models, we observed an increased risk of prelabor rupture of membranes (aHR 1.54, 95% CI 1.27-1.87), spontaneous preterm birth (aHR 1.79, 95% CI 1.37-2.34), fetal growth restriction associated (aHR 2.04; 95% CI 1.72, 2.43), and postpartum hemorrhage (aHR 1.98, 95% CI 1.53-2.57) with prenatal SARS-CoV-2 infection (**Table 2**). We additionally observed increased risk of clinician-initiated events, including labor induction (aHR 1.99, 95% CI 1.74-2.27), cesarean section (aHR: 1.99, 95% CI 1.71-2.31), and clinician-initiated preterm birth (aHR 2.88, 95% CI 1.93-4.30). There was no association or a reduced association between SARS-CoV-2 infection and risk of hyperemesis (aHR 0.87, 95% CI 0.56-1.36), antepartum hemorrhage (aHR 0.65, 95% CI 0.42-1.01), gestational diabetes (aHR 0.73, 95% CI 0.55-0.97), pre-eclampsia (aHR 0.88, 95% CI 0.56-1.37), placental abruption (aHR 1.19, 95% CI 0.53-2.69), or stillbirth (aHR 1.55, 95% CI 0.52-4.61). We observed similar estimates for the sub-cohort of pregnancies conceived between 1 January and 30 April 2020. In this sub-cohort, the risk of miscarriage (aHR 1.27, 95% CI 0.86-1.87) was similar for SARS-CoV-2-infected pregnancies compared to uninfected. Induced abortion was 2.6 times higher (95% CI 1.17-5.78) among pregnancies infected with SARS-CoV-2 compared to uninfected

pregnancies. Effect estimates were similar for SARS-CoV-2 infections whether they were identified in first, second, or third trimester (**Table 3**). We observed indications of a dose-response relationship between severity of SARS-CoV-2 infection and risk of adverse pregnancy outcomes, with a trend toward higher risk associated with infections classed as “severe.” However, we identified a small number of “severe” infections (n=91) and this resulted in low precision in our effect estimates (**Figure 2**).

When we evaluated pregnancy outcomes for those who were tested for SARS-CoV-2 during pregnancy (n=5,644), we observed similar results to our primary analysis (**eTable 4**). We observed no associations for prenatal SARS-CoV-2 infections occurring near delivery. However, increased risks of fetal growth restriction (aHR 1.92, 95% CI 1.61-2.28), spontaneous preterm birth (aHR 1.70, 95% CI 1.30-2.24), clinician-initiated preterm birth (aHR 2.76, 95% CI 1.84-4.15), cesarean section (aHR 1.88, 95% CI 1.62-2.19), and postpartum hemorrhage (aHR 1.83, 95% CI 1.41-2.38) were observed following SARS-CoV-2 infection occurring more than 3 days prior to delivery (**eTable 5**).

Discussion

Based on clinical health information from a large cohort of pregnancies during the COVID-19 pandemic in the US, results suggest that 3% of pregnant individuals who delivered between March and January 2021 experienced a SARS-CoV-2 infection, and infection was associated with increased risks of poor pregnancy outcomes. These findings suggest prevention of SARS-CoV-2 infection during pregnancy may confer maternal and fetal health benefits. In addition to handwashing and social distancing measures, with the availability of highly efficacious vaccines [15-17], guidelines encouraging vaccination of pregnant individuals [18], and early results suggesting mRNA vaccine safety in pregnancy [19], effective prevention of maternal SARS-CoV-2 infection is possible.

Our findings corroborate those of the living systematic review [4] and a recent review of systematic reviews [20], indicating that preterm birth rates, especially those medically indicated, are higher among pregnancies with SARS-CoV-2 infection. The recent review of systematic reviews by Papapanou et al (2021) identified similar findings based on their summary of evidence from smaller,

regional studies [20]. Although the relationship between preterm birth and the COVID-19 pandemic has been debated [21], our findings from a large US cohort support increased risk of preterm birth associated with SARS-CoV-2 infection during pregnancy. We additionally identified increased risks of fetal growth restriction and prelabor rupture of membranes - pregnancy outcomes which could implicate the role of ischemic placental pathology. Several studies have observed evidence of placental injury and vascular malperfusion in SARS-CoV-2 infected pregnancies, even when infection was asymptomatic.[22-25] While our data offer additional support for this potential mechanism, further evidence elucidating biological mechanisms through which SARS-CoV-2 infection may impact pregnancy health would be useful.

In addition to aligning with pooled analyses of multiple smaller studies [4], our results contribute several additional important points of knowledge. First, few previous studies have been powered to independently evaluate the risk of stillbirth. Higher rates of stillbirth have been reported in Israel during their first wave of the pandemic [26], and prospective cohort studies have identified higher rates of stillbirth and neonatal mortality, potentially associated with decreases in quality of clinical care [27]. A large systematic review estimated the pooled risk of stillbirth from 5,794 participants in nine studies to be 2.84 (95% CI 1.25, 6.45). However, recent surveillance data from the UK suggested there was no increase in stillbirths during their first COVID-19 epidemic (prior to June 30, 2020) [28]. To our knowledge, our study is the largest single comparative epidemiological study to date to evaluate the risk of stillbirth associated with SARS-CoV-2 infection [4]. We observed no association between the risk of stillbirth with SARS-CoV-2 infection. However, since we identified only 401 stillbirths, further large-scale evaluation remains important.

Second, few studies have been able to assess early pregnancy outcomes [4]. Examination of fetal tissues from patients infected in early pregnancy has shown that congenital SARS-CoV-2 infection is possible during first trimester, with documented damage to the placenta and fetal organs following hyperinflammatory processes [25]. However, epidemiological evidence has not supported an association with miscarriage. A recent Danish cohort study of pregnant individuals diagnosed with COVID-19 during the first trimester of pregnancy found no difference in nuchal translucency

thickness for those who tested positive compared to those who tested negative for SARS-CoV-2 and there was no increased risk of pregnancy loss [29]. However, these data were based on a small number of SARS-CoV-2 infections (n=18) with only one event identified among SARS-CoV-2 positive pregnancies. Our cohort, drawing from a larger number of infected pregnancies (n=2,655) corroborate those of the Danish study, suggesting no association between COVID-19 infection and risk of miscarriage.

Finally, due to the large sample of cases, we were able to evaluate pregnancy outcomes by trimester of exposure to COVID-19. Risk of preterm birth was elevated regardless of trimester of infection and more commonly among pregnancies where infection occurred weeks prior to delivery. Previous studies of SARS-CoV-2 infected pregnancies have suggesting a mechanistic role of placenta [30], outlining a biologically plausible pathway from infection with SARS-CoV-2 virus to preterm birth, fetal growth restriction and other adverse outcomes [24, 25, 31]. However, further research into mechanisms involved in exposure to SARS-CoV-2 early in pregnancy is needed.

Despite the novel contributions to the literature, our study is not without limitations. First, we relied on diagnostic coding and laboratory testing records to identify a large sample of pregnant individuals with a record of SARS-CoV-2 infection. While this allowed us the opportunity to draw from a large sample using medical data, it is possible that we included asymptomatic cases. The inclusion of asymptomatic cases in the epidemiological evaluation of COVID-19 and perinatal health has been debated [32]. We attempted to address this limitation by evaluating severe cases of COVID-19, which would have been exhibiting severe symptoms of infection. Second, although the maternal mortality rate identified in our cohort was higher than the national average in 2019 (32 per 100,000 live births in our cohort vs. 20 per 100,000 in 2019 in the US [33]), the small number of deaths precluded us from more detailed analyses. Several studies have identified higher rates of maternal mortality associated with SARS-CoV-2 infection during pregnancy[34, 35], and this remains an important maternal health outcome for consideration in future studies. Second, our analysis drew from a large data repository of longitudinal clinical health information, but data were restricted to commercially insured pregnant individuals. As a result, these results may not be generalizable to the entire

population. Replication among publicly insured and uninsured populations would be useful. Finally, this was an observational study, and although we employed multiple techniques to avoid the influence of confounding and other biases, we cannot entirely exclude the possible influence of unobserved confounding in our results.

Conclusions

Few large-scale studies have evaluated the risk of adverse pregnancy outcomes following maternal SARS-CoV-2 infection. Results from our cohort of 78,283 pregnancies occurring during the COVID-19 pandemic in the US support previous suggestions of fetal harm following infection. In combination with evidence suggesting pregnant individuals are at higher risk of severe COVID-19 disease [1, 36], prevention of COVID-19 disease during pregnancy should be a priority. Social distancing, routine handwashing, and immunization could reduce the risk of maternal infection and associated adverse pregnancy outcomes.

Accepted Manuscript

References

1. 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**; 69:769-75.
2. 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**; 69:1641-7.
3. 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.
4. 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.
5. Jering KS, Claggett BL, Cunningham JW, et al. Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19. *JAMA Intern Med* **2021**.
6. Update to living systematic review on covid-19 in pregnancy. *BMJ* **2021**; 372:n615.
7. Engjom H, Aabakke AJM, Klungsoyr K, et al. COVID-19 in pregnancy – characteristics and outcomes of pregnant women admitted to hospital because of SARS-CoV-2 infection in the Nordic countries. *medRxiv* **2021**:2021.02.05.21250672.
8. Adhikari EH, Moreno W, Zofkie AC, et al. Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *JAMA Netw Open* **2020**; 3:e2029256.
9. 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.
10. Neophytou AM, Kioumourtzoglou MA, Goin DE, Darwin KC, Casey JA. Educational note: addressing special cases of bias that frequently occur in perinatal epidemiology. *Int J Epidemiol* **2021**; 50:337-45.
11. Liew Z, Olsen J, Cui X, Ritz B, Arah OA. Bias from conditioning on live birth in pregnancy

- cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. *Int J Epidemiol* **2015**; 44:345-54.
12. OptumLabs. OptumLabs and OptumLabs Data Warehouse (OLDW) Descriptions and Citation. Eden Prairie, MN, **July 2020**.
 13. Ailes EC, Simeone RM, Dawson AL, Petersen EE, Gilboa SM. Using insurance claims data to identify and estimate critical periods in pregnancy: An application to antidepressants. *Birth Defects Res A Clin Mol Teratol* **2016**; 106:927-34.
 14. Honaker J, King G, Blackwell M. Package 'Amelia'. Available at: <https://cran.r-project.org/web/packages/Amelia/Amelia.pdf>. Accessed April 30 2021.
 15. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* **2021**; 384:403-16.
 16. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* **2020**; 383:2603-15.
 17. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med* **2020**; 383:2439-50.
 18. Adhikari EH, Spong CY. COVID-19 Vaccination in Pregnant and Lactating Women. *JAMA* **2021**; 325:1039-40.
 19. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med* **2021**; 384:2272-82.
 20. Papananou 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**; 18:596.
 21. Arnaez J, Ochoa-Sangrador C, Caserío S, et al. Lack of changes in preterm delivery and stillbirths during COVID-19 lockdown in a European region. *Eur J Pediatr* **2021**:1-6.
 22. Celik E, Vatansever C, Ozcan G, et al. Placental deficiency during maternal SARS-CoV-2 infection. *Placenta* **2021**; 117:47-56.
 23. Dumont S, Balduyck J, Reynders M, Vanwalleghem L, Lebbe B. Acute SARS-CoV-2 alpha variant infection leading to placental insufficiency and fetal distress. *J Med Virol* **2021**.

24. Oltean I, Tran J, Lawrence S, et al. Impact of SARS-CoV-2 on the clinical outcomes and placental pathology of pregnant women and their infants: A systematic review. *Heliyon* **2021**; 7:e06393.
25. Valdespino-Vázquez MY, Helguera-Repetto CA, León-Juárez M, et al. Fetal and placental infection with SARS-CoV-2 in early pregnancy. *J Med Virol* **2021**; 93:4480-7.
26. Mor M, Kugler N, Jauniaux E, et al. Impact of the COVID-19 Pandemic on Excess Perinatal Mortality and Morbidity in Israel. *Am J Perinatol* **2021**; 38:398-403.
27. Kc A, Gurung R, Kinney MV, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. *Lancet Glob Health* **2020**; 8:e1273-e81.
28. Stowe J, Smith H, Thurland K, Ramsay ME, Andrews N, Ladhani SN. Stillbirths During the COVID-19 Pandemic in England, April-June 2020. *JAMA* **2021**; 325:86-7.
29. la Cour Freiesleben N, Egerup P, Hviid KVR, et al. SARS-CoV-2 in first trimester pregnancy: a cohort study. *Hum Reprod* **2021**; 36:40-7.
30. 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**; 127:1548-56.
31. Shende P, Gaikwad P, Gandhewar M, et al. Persistence of SARS-CoV-2 in the first trimester placenta leading to transplacental transmission and fetal demise from an asymptomatic mother. *Hum Reprod* **2021**; 36:899-906.
32. Chisholm RH, Campbell PT, Wu Y, Tong SYC, McVernon J, Geard N. Implications of asymptomatic carriers for infectious disease transmission and control. *R Soc Open Sci* **2018**; 5:172341.
33. Hoyert DL. Maternal mortality rates in the United States, 2019. *NCHS Health E-Stats* **2021**.
34. Scheler CA, Discacciati MG, Vale DB, Lajos GJ, Surita F, Teixeira JC. Mortality in pregnancy and the postpartum period in women with severe acute respiratory distress syndrome related to COVID-19 in Brazil, 2020. *Int J Gynaecol Obstet* **2021**; 155:475-82.
35. Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal

and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health* **2021**; 9:e759-e72.

36. Panagiotakopoulos L, Myers TR, Gee J, et al. SARS-CoV-2 Infection Among Hospitalized Pregnant Women: Reasons for Admission and Pregnancy Characteristics - Eight U.S. Health Care Centers, March 1-May 30, 2020. *MMWR Morb Mortal Wkly Rep* **2020**; 69:1355-9.

Accepted Manuscript

Footnote Page

Funding statement

This work received no direct financial support; however, access to study data was financially supported by OptumLabs® and University of California Los Angeles. The WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health. The funder had no influence in the design or implementation of the study or the decision to publish the study findings.

Author access to data

During the conduct of the study, the first author (AKR) had full access to the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis; however, the authors do not have ongoing access to the data analyzed in this study, nor do they have permission to share the study data with other researchers.

Author Contribution Statement

AKR extracted and prepared data and oversaw all aspects of project implementation. OA and SS contributed to the study design. OA, SS and DBF contributed to the development of the analytic plan. AKR performed the statistical analyses and prepared study results. AKR, OA, DBF and SS contributed to the interpretation of findings. AKR led the drafting of the report, and all co-authors contributed to revising of the report and approved the final version.

Declaration of interests

AKR, OA, DBF, and SS have no conflicts of interest to disclose.

* Results were accepted for presentation at the 2021 Annual Meeting of the Society for Epidemiologic Research and the 2021 Annual Conference of the American Public Health Association.

**Corresponding author: Annette Regan, School of Nursing and Public Health, University of San Francisco, 480 S Batavia Street, Orange CA 98484; +1 714.221.6213; akregan@usfca.edu

FIGURE LEGENDS

Figure 1. Gestational age at SARS-CoV-2 infection during pregnancy, by infection severity – March 2020 to January 2021, United States.

NOTE: Severe COVID-19 was defined as diagnosed infections coinciding with admission to intensive care unit, requirement for invasive mechanical ventilation or extracorporeal membrane oxygenation treatment, or diagnosis with acute respiratory distress syndrome. Mild COVID-19 was defined as diagnosed infections with no record of such treatment.

Figure 2. Risk of adverse pregnancy outcomes associated with SARS-Cov-2 infection, by severity of infection – March 2020 to January 2021, United States.

NOTE: Severe COVID-19 was defined as SARS-CoV-2 infections coinciding with admission to intensive care unit, requirement for invasive mechanical ventilation or extracorporeal membrane oxygenation treatment, or diagnosis with acute respiratory distress syndrome. Mild COVID-19 was defined as SARS-CoV-2 infections with no record of such treatment.

Accepted Manuscript

Table 1. SARS-CoV-2 infection among US pregnant individuals, by sociodemographic and health factors (N=78,283) – March 2020 to January 2021, United States.

Characteristic	<u>SARS-CoV-2 Infection^a</u>				<u>Proportionate Severity^a</u>		
	Total N	N	% (95% CI)	RR (95% CI) ^b	n	% (95% CI)	RR (95% CI) ^b
Maternal age							
<24 years	5,684	293	5.1 (4.6-5.8)	1.61 (1.43-1.79)	16	5.5 (3.1-8.7)	0.53 (0.01-1.23)
25-29 years	19,496	819	4.2 (3.9-4.5)	1.37 (1.20-1.53)	20	2.4 (1.5-3.7)	0.30 (0.01-0.99)
30-34 years	29,207	879	3.0 (2.8-3.2)	0.98 (0.81-1.15)	28	3.2 (2.1-4.6)	0.39 (0.01-1.01)
35-39 years	18,348	503	2.7 (2.5-3.0)	0.91 (0.73-1.08)	14	2.8 (1.5-4.6)	0.34 (0.01-1.07)
≥40 years	5,548	161	2.9 (2.5-3.4)	Reference	13	8.1 (4.4-13.4)	Reference
Race/ethnicity							
White, non-Hispanic	48,969	1,408	2.9 (2.7-3.0)	Reference	39	2.8 (2.0-3.8)	Reference
Black, non-Hispanic	9,205	403	4.4 (4.0-4.8)	1.54 (1.43-1.65)	16	4.0 (2.3-6.4)	1.38 (0.80-1.96)
Hispanic	13,013	647	5.0 (4.6-5.4)	1.73 (1.64-1.82)	25	3.9 (2.5-5.7)	1.40 (0.92-1.88)
Other race	7,096	197	2.8 (2.4-3.2)	0.97 (0.83-1.12)	11	5.6 (2.8-9.8)	1.87 (1.20-2.55)
Education							
≤High school graduate	16,771	742	4.4 (4.1-4.7)	1.50 (1.40-1.61)	27	3.6 (2.4-5.3)	0.98 (0.44-1.52)

Some college	40,135	1,290	3.2 (3.0-3.4)	1.10 (1.01-1.19)	41	3.2 (2.3-4.3)	0.86 (0.37-1.36)
≥College graduate	21,377	623	2.9 (2.7-3.1)	Reference	23	3.7 (2.3-5.5)	Reference
Residence							
Metropolitan	70,452	2,337	3.3 (3.2-3.5)	Reference
Micropolitan	4,297	172	4.0 (3.4-4.6)	1.19 (1.03-1.34)
Small town/Rural	3,534	146	4.1 (3.5-4.8)	1.22 (1.06-1.39)
Household income							
<\$40,000	45,379	1,475	3.3 (3.1-3.4)	Reference	39	2.6 (1.9-3.6)	Reference
\$40-74,999	15,564	606	3.9 (3.6-4.2)	1.20 (1.12-1.30)	32	5.3 (3.6-7.4)	1.98 (1.52-2.43)
≥75,000	17,340	574	3.3 (3.1-3.6)	1.02 (0.93-1.11)	20	3.5 (2.1-5.3)	1.33 (0.80-1.85)
Medical conditions							
Any medical condition	9,972	390	3.9 (3.5-4.3)	1.18 (1.08-1.29)	32	8.2 (5.7-11.4)	3.31 (2.90-3.73)
Asthma	5,294	208	3.9 (3.4-4.5)	1.17 (1.03-1.31)	18	8.7 (5.2-13.3)	3.12 (2.62-3.62)
Chronic hypertension	3,652	146	4.0 (3.4-4.7)	1.20 (1.04-1.36)	14	9.6 (5.3-15.6)	3.34 (2.79-3.88)
Immune disorder	160	13	8.1 (4.4-13.5)	2.42 (1.90-2.94)	<11
No medical condition	68,311	2,265	3.3(3.2-3.5)	Reference	59	2.6 (2.0-3.3)	Reference
Timing of pregnancy							

Conception date prior to Jan 2020	49,062	976	2.0 (1.9-2.1)	Reference	45	4.6 (3.4-6.1)	Reference
Conception date Jan – Apr 2020	29,221	1,679	5.7 (5.5-6.0)	3.44 (3.36-3.51)	46	2.7 (2.0-3.6)	0.59 (0.19-1.00)

Abbreviations: RR, relative risk; CI, confidence interval

.. indicates insufficient data to estimate.

^aCOVID-19 infection was defined as a diagnosis of COVID-19 or a positive SARS-CoV-2 test; proportionate severity was defined as the proportion of COVID-19 cases classed as “severe.”

Severe COVID-19 infection was defined as a COVID-19 infection coinciding with admission to intensive care unit, requirement for invasive mechanical ventilation or extracorporeal membrane oxygenation treatment, or diagnosis with acute respiratory distress syndrome.

^bRelative risk calculated using Poisson regression with robust standard errors (using sandwich estimator) and adjusting for week of pregnancy conception (cubic spline).

Table 2. Pregnancy outcomes following SARS-CoV-2 infection, by date of conception (N=78,283) – March 2020 to January 2021, United States.

Pregnancy outcome, by date of conception	SARS-CoV-2 infection^a No. (%)	No SARS-CoV-2 infection^a No. (%)	HR (95% CI)^b	aHR (95% CI)^b
<i>Conception before 30 Apr 2020</i>				
Hyperemesis	124 (4.7)	3,354 (4.4)	1.00 (0.65, 1.54)	0.87 (0.56, 1.36)
Antepartum hemorrhage	199 (7.5)	4,684 (6.2)	0.74 (0.48, 1.15)	0.65 (0.42, 1.01)
Gestational diabetes	291 (11.4)	7,807 (11.6)	0.77 (0.58, 1.03)	0.73 (0.55, 0.97)
Preeclampsia	123 (4.8)	3,320 (4.9)	0.99 (0.64, 1.53)	0.88 (0.56, 1.37)
Prelabor rupture of membranes	290 (11.4)	8,426 (12.5)	1.62 (1.34, 1.97)	1.54 (1.27, 1.87)
Placental abruption	38 (1.5)	783 (1.2)	1.42 (0.62, 3.28)	1.19 (0.53, 2.69)
Induction of labor	766 (30.0)	18,553 (27.6)	2.07 (1.82, 2.36)	1.99 (1.74, 2.27)
Cesarean section	430 (16.8)	11,856 (17.6)	1.93 (1.66, 2.25)	1.99 (1.71, 2.31)
Preterm birth	199 (7.8)	4,431 (6.6)	2.37 (1.89, 2.98)	2.07 (1.65, 2.61)
Clinician-initiated preterm birth	58 (2.4)	1,046 (1.6)	3.41 (2.30, 5.07)	2.89 (1.94, 4.31)
Spontaneous preterm birth	141 (5.6)	3,385 (5.1)	2.06 (1.57, 2.72)	1.83 (1.39, 2.41)

Fetal growth restriction	310 (12.1)	7,845 (11.7)	2.22 (1.87, 2.63)	2.04 (1.72, 2.43)
Stillbirth	14 (0.5)	387 (0.6)	1.76 (0.59, 5.23)	1.55 (0.52, 4.61)
Postpartum hemorrhage	155 (4.7)	3,354 (4.4)	2.09 (1.62, 2.72)	2.03 (1.56, 2.63)
<i>Conception 1 Jan – 30 Apr 2020</i>				
Miscarriage	80 (4.7)	5,090 (18.5)	1.63 (1.18, 2.26)	1.27 (0.86, 1.87)
Induced abortion	14 (0.8)	1,070 (3.9)	3.55 (1.66, 7.55)	2.60 (1.17, 5.78)
Hyperemesis	86 (5.1)	1,128 (4.1)	1.08 (0.67, 1.74)	0.90 (0.55, 1.47)
Antepartum hemorrhage	140 (8.3)	1,654 (6.0)	0.86 (0.54, 1.36)	0.75 (0.48, 1.19)
Gestational diabetes	172 (10.9)	2,658 (12.4)	0.74 (0.53, 1.03)	0.69 (0.50, 0.96)
Preeclampsia	85 (5.4)	1,086 (5.1)	1.08 (0.67, 1.74)	0.91 (0.55, 1.48)
Prelabor rupture of membranes	187 (11.8)	2,780 (13.0)	1.57 (1.25, 1.97)	1.46 (1.16, 1.83)
Placental abruption	28 (1.7)	260 (1.2)	1.85 (0.80, 4.26)	1.42 (0.63, 3.20)
Induction of labor	477 (30.1)	5,946 (27.8)	1.92 (1.60, 2.30)	1.84 (1.59, 2.12)
Cesarean section	282 (17.8)	3,753 (17.5)	1.92 (1.60, 2.30)	1.85 (1.54, 2.22)

Preterm birth	136 (8.6)	1,622 (7.6)	2.15 (1.64, 2.81)	1.72 (1.31, 2.27)
Clinician-initiated preterm birth	46 (3.1)	433 (2.2)	2.93 (1.86, 4.60)	2.15 (1.34, 3.47)
Spontaneous preterm birth	90 (5.8)	1,189 (5.7)	1.88 (1.35, 2.62)	1.55 (1.11, 2.18)
Fetal growth restriction	196 (12.4)	2,651 (12.4)	2.01 (1.61, 2.51)	1.84 (1.47, 2.29)
Stillbirth	<11	148 (0.7)
Postpartum hemorrhage	97 (6.1)	1,197 (5.6)	2.06 (1.53, 2.77)	1.96 (1.46, 2.62)

Abbreviations: RR, relative risk; CI, confidence interval

.. indicates insufficient data to estimate.

^a COVID-19 infection was defined as a diagnosis of COVID-19 or a positive SARS-CoV-2 test.

^b Cox proportional hazard model comparing risk of outcome among COVID-19 infected pregnancies vs. uninfected pregnancies, treating COVID-19 infection as a time-varying exposure. Adjusted models controlled for maternal age, race/ethnicity, annual household income, presence of a pre-existing medical condition (yes/no), and week of pregnancy conception (cubic spline).

Table 3. Risk of pregnancy outcomes associated with prenatal SARS-CoV-2 infection (N=78,283), by trimester of infection – March 2020 to January 2021, United States.

Pregnancy outcome	<u>First Trimester (n=171)</u>		<u>Second Trimester (n=513)</u>		<u>Third Trimester (n=1,971)</u>	
	HR (95% CI) ^a	aHR (95% CI) ^a	HR (95% CI) ^a	aHR (95% CI) ^a	HR (95% CI) ^a	aHR (95% CI) ^a
Prelabor rupture of membranes	2.11 (1.08-4.13)	1.96 (1.00-3.82)	1.38 (0.97-1.97)	1.30 (0.91-1.84)	1.68 (1.32-2.15)	1.59 (1.25-2.04)
Induction of labor	2.74 (1.40-5.34)	2.57 (1.32-4.99)	1.75 (1.40-2.18)	1.67 (1.34-2.08)	2.15 (1.84-2.51)	2.05 (1.74-2.42)
Cesarean section	2.18 (1.24-3.81)	2.08 (1.19-3.64)	1.74 (1.29-2.33)	1.72 (1.28-2.32)	1.99 (1.65-2.40)	2.09 (1.74-2.50)
Preterm birth	2.15 (1.44-3.20)	1.85 (1.24-2.76)	2.68 (2.00-3.59)	2.38 (1.78-3.19)
Clinician-induced preterm birth	3.22 (1.74-5.96)	2.67 (1.44-4.96)	3.93 (2.25-6.87)	3.38 (1.93-5.90)
Spontaneous preterm birth	1.74 (1.03-2.94)	1.51 (0.90-2.56)	2.40 (1.71-3.35)	2.16 (1.54-3.02)
Fetal growth restriction	2.95 (1.42-6.14)	2.53 (1.21-5.28)	1.97 (1.41-2.75)	1.77 (1.26-2.47)	2.25 (1.83-2.76)	2.09 (1.71-2.57)
Postpartum hemorrhage	2.20 (1.34-3.59)	2.11 (1.28-3.46)	2.13 (1.56-2.91)	2.08 (1.52-2.84)

.. Insufficient data to estimate.

^aCox proportional hazard model comparing risk of outcome among COVID-19 infected pregnancies vs. uninfected pregnancies, treating COVID-19 infection as a time-varying exposure. Adjusted models controlled for maternal age, race/ethnicity, household income, presence of a pre-existing medical condition (yes/no), and week of pregnancy conception (cubic spline).

Figure 1

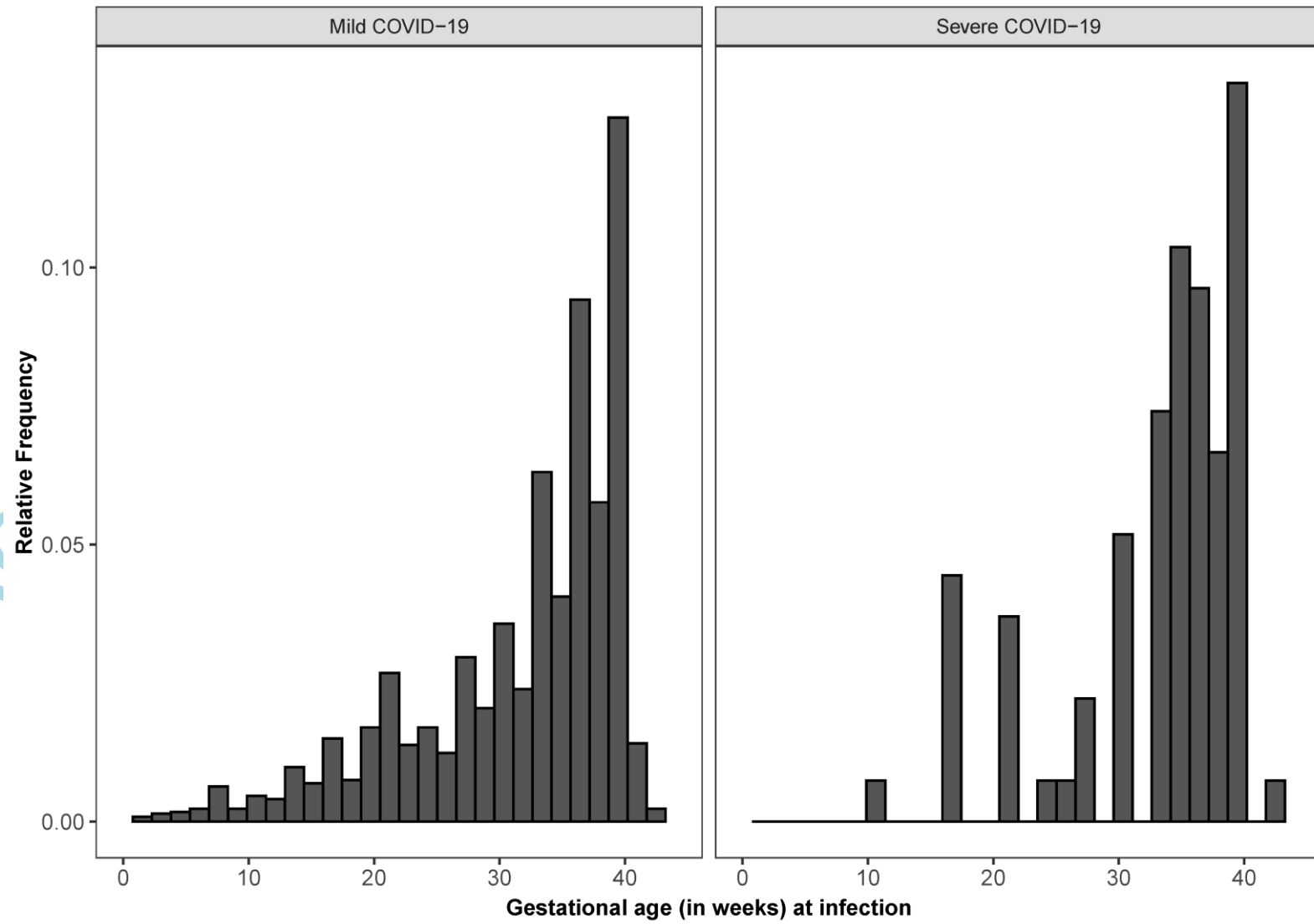


Figure 2

