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An Update on Coronavirus Disease 2019 (COVID-19) and Pregnancy

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Abstract

Physiologic, mechanical and immunologic alterations in pregnancy could potentially affect susceptibility to and severity of COVID-19 during pregnancy. Due to lack of comparable incidence data and challenges with disentangling differences in susceptibility from different exposure risks, data are insufficient to determine whether pregnancy increases susceptibility to SARS-CoV-2 infection. Data support pregnancy as a risk factor for severe disease associated with COVID-19; some of the best evidence comes from the Centers for Disease Control and Prevention's (CDC's) COVID-19 surveillance system, which reported that pregnant persons were more likely to be admitted to an intensive care unit (ICU), require invasive ventilation, require extracorporeal membrane oxygenation, and die compared with nonpregnant women of reproductive age. Although intrauterine transmission of SARS-CoV-2 has been documented, it appears to be rare, possibly related to low levels of SARS-CoV-2 viremia and decreased co-expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) needed for SARS-CoV-2 entry into cells in the placenta. Evidence is accumulating that SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes including preeclampsia, preterm birth, and stillbirth, especially among pregnant persons with severe COVID-19 disease. In addition to the direct impact of COVID-19 on pregnancy outcomes, there is evidence that the pandemic and its effects on healthcare systems have had adverse effects on pregnancy outcomes, such as increased stillbirths and maternal deaths. These trends may represent widening disparities and an alarming reversal of recent improvements in maternal and infant health. All three COVID-19 vaccines currently available under an Emergency Use Authorization by the United States Food and Drug Administration can be administered to pregnant or lactating persons, with no preference for vaccine type. Although

safety data in pregnancy are rapidly accumulating and no safety signals in pregnancy have been detected, additional information about birth outcomes, particularly among persons vaccinated earlier in pregnancy, are needed.

Since identification of the first cases of Coronavirus disease 2019 (COVID-19) caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December of 2019, the virus has spread rapidly throughout the world. Worldwide, over 207 million persons have been infected, with more than 4 million deaths. In the United States alone, over 620,000 persons have died of COVID-19, as of August 15, 2021.[1] In addition to the devastating degree of morbidity and mortality caused by SARS-CoV-2, the virus and efforts to mitigate its transmission have caused unprecedented economic and social disruption. Early on, many questions arose regarding the effects of COVID-19 on pregnant persons, including whether pregnancy increased susceptibility to SARS-CoV-2 infection, whether pregnant persons were more likely to have severe disease, and whether SARS-CoV-2 infection increased the risk for adverse pregnancy and neonatal outcomes. Here we review the latest information on SARS-CoV-2 infection during pregnancy, including what is known about COVID-19 vaccines during pregnancy and lactation.

Susceptibility, Severity and Clinical Course

Although physiologic, mechanical and immunologic alterations in pregnancy could potentially affect susceptibility to COVID-19 during pregnancy, limited data are available to address this issue. Many studies have reported the prevalence of SARS-CoV-2 infection among pregnant persons presenting to labor and delivery with estimates ranging from 3-20%.[2,3] However, it is difficult to compare these rates to other populations since universal screening is not commonly conducted. One study compared universal pre-procedural testing among asymptomatic surgical patients to obstetric patients presenting in labor. The asymptomatic infection rate was 15-fold higher in obstetric patients compared with surgical patients, even after adjustment for age, race and sex.[4] In a report from the Centers for Disease Control and

Prevention (CDC), the number of cases of laboratory-confirmed SARS-CoV-2 infection was higher than expected among pregnant persons; among women of reproductive age infected with SARS-CoV-2, 9% were pregnant compared to an estimated 5% of women aged 15-44 years who are pregnant at any point in time. However, there was a large amount of missing data, and the investigators were unable to adjust for potentially different testing and ascertainment rates, given more widespread screening of asymptomatic pregnant persons.[5] Similarly, a study from Washington state reported higher infection rates among pregnant patients (13.9 per 1000 deliveries) compared with adults aged 20-39 years (7.3 per 1000 persons); this study was also unable to account for differential testing rates in pregnant compared to nonpregnant persons.[6] Even with better incidence data, disentangling differences in susceptibility from different exposure risks is challenging; to address susceptibility, ideally incident rates of infection among pregnant and nonpregnant women of the same age with similar exposures to SARS-CoV-2 would be compared. In summary, data are insufficient to conclude whether or not pregnancy increases susceptibility to SARS-CoV-2.

Similar to what is observed in nonpregnant persons, SARS-CoV-2 infection is more frequent among persons who live in socially and economically disadvantaged settings. In a report from New York City, the likelihood of SARS-CoV-2 infection was higher in pregnant persons who lived in buildings with lower mean assessed values and more residential units, and in neighborhoods with lower median household incomes, higher unemployment rates, large household sizes, and greater household crowding.[7] In a report from Atlanta, higher rates of SARS-CoV-2 infection among pregnant persons were associated with Hispanic ethnicity, lack of health insurance, high neighborhood density, and paradoxically, smaller household size.[8]

Several studies support that COVID-19 causes more severe disease during pregnancy. While many early reports lacked appropriate comparison groups, later studies have compared pregnant to nonpregnant women, adjusted by age and comorbidities. Some of the best data come from the CDC's COVID-19 surveillance system, which included over 400,000 persons of reproductive age with symptomatic COVID-19 and adjusted for age, race/ethnicity, and underlying medical conditions. Compared to nonpregnant women, pregnant persons were three times more likely to be admitted to an intensive care unit (ICU) (10.5 vs 3.9 per 1,000), 2.9 times more likely to require invasive ventilation (2.9 vs. 1.1 per 1,000 cases), 2.4 times more likely to require extracorporeal membrane oxygenation (0.7 vs. 0.3 per 1,000 cases), and 1.7 times more likely to die (1.5 vs. 1.2 per 1,000 cases).[9] (Figure 1) Additional studies from the United States and Europe report similar results. For example, a study from four European hospitals compared pregnant and nonpregnant women matched by propensity score for age, body mass index, and comorbidities and found an increased risk of severe disease during pregnancy including an increased risk of ICU admission (primary outcome) as well as increased risks of hospital admission, need for oxygen therapy, and need for endotracheal intubation (secondary outcomes).[10] A study from Washington state found an increased risk of hospitalization and an elevated case-fatality rate among pregnant persons compared with nonpregnant persons of similar age.[11] Increased risk for disease severity in pregnancy may be due to mechanical changes such as decreased lung volume as the fetus grows, immunologic changes, and an increased risk for thromboembolic disease.[9]

Risk factors for severe disease have been shown to be similar among pregnant and nonpregnant persons. Data from the United Kingdom's Obstetric Surveillance System found that black race, older age (≥35 years), and overweight/obesity were risk factors for hospitalization

among pregnant persons.[12] Similarly, data from the Surveillance for Emergency Threats to Mothers and Babies Network (SET-NET) in the United States found that older age and underlying medical conditions such as obesity, chronic lung disease, chronic hypertension, and pregestational diabetes mellitus were associated with more severe COVID-19 in pregnancy.[13] A report from the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network found that older maternal age, higher body mass index, and pre-existing comorbidities defined as asthma, chronic obstructive pulmonary disease, chronic hypertension, or pregestational diabetes mellitus, were associated with more severe COVID-19 disease during pregnancy.[14] Similar to nonpregnant persons, certain chronic medical conditions may lead to increased COVID-19 disease severity in a variety of ways such as weakening the immune system, increasing inflammation, or reducing the ability to withstand infection. Regarding clinical course, a prospective registry of pregnant patients with symptomatic COVID-19 found that 25% of pregnant patients reported persistent symptoms 8 or more weeks from symptom onset.[15] Whether pregnancy confers an increased risk for a prolonged course of disease requires additional study.

Transmission of SARS-CoV-2 to the Fetus and Neonate

When a new virus emerges, a critical question is whether the virus can cross the placenta and cause direct adverse effects on the fetus, as has been seen with several other pathogens (e.g., Zika, cytomegalovirus, rubella). Transmission of pathogens can occur during pregnancy and before onset of labor (intrauterine); during labor and delivery (intrapartum); or following birth, either through breastfeeding or through contact with the mother or others (postpartum). Several systems have been developed to categorize perinatal SARS-CoV-2 transmission and they share some common features including requiring evidence of maternal infection, fetal exposure, and

persistence of infection in the fetus or neonate.[16-18] Although a few cases of intrauterine SARS-CoV-2 transmission have been carefully documented,[19] transmission appears to be rare.[18] Several factors may help explain why transmission appears to be rare. For intrauterine transmission of a viral pathogen to occur, the pathogen needs to reach and cross the placenta,[20] and SARS-CoV-2 infection is not associated with high levels of viremia.[21] In addition, the placenta may not co-express high levels of the primary factors that facilitate SARS-CoV-2 entry into cells, angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2)[21-23] although data regarding expression of these factors is not entirely consistent.[24,25]

Most SARS-CoV-2 infections identified among infants after birth are due to exposure to infected caregivers. However, data on the safety of a SARS-CoV-2-infected mother breastfeeding are reassuring. Replication-competent SARS-CoV-2 has not been detected in breastmilk,[26] although breastmilk samples are occasionally PCR-positive.[27] An observational cohort of 116 SARS-CoV-2-infected mothers who reported consistent use of surgical masks, hand hygiene, and breast cleansing all safely breastfed without SARS-CoV-2 transmission.[28] In addition, a systematic review found no increase in late postnatal transmission (defined as occurring after 72 hours of life) associated with breastfeeding; however, an increased risk of late postnatal transmission was observed when infants were not separated from their infected mothers after birth.[29] This possible increased risk must be weighed against the known benefits of mother-infant bonding and minimal risk of severe infant illness. Most guidelines support rooming in of the newborn with an infected mother, particularly when the mother is afebrile and asymptomatic.[30,31]

Pregnancy Outcomes

Although it appears that SARS-CoV-2 rarely is transmitted transplacentally to the fetus, evidence is accumulating that SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes. A systematic review and meta-analysis of relatively high-quality studies with appropriate comparison groups found an increased risk of preeclampsia, preterm birth, and stillbirth among pregnant persons with SARS-CoV-2 infection compared with those without SARS-CoV-2 infection.[32] Among pregnant persons with COVID-19, severe disease was associated with preeclampsia, preterm birth, gestational diabetes, and low birth weight compared to those with mild disease.[32] Two studies published after the meta-analysis found similar findings. A multi-national cohort study found pregnant persons with COVID-19 were at increased risk for preeclampsia/eclampsia and preterm birth compared to pregnancies without COVID-19.[33] In an observational study of 1219 pregnant patients testing positive for SARS-CoV-2, those with severe disease were at increased of cesarean delivery, hypertensive disorders of pregnancy, and preterm birth compared to asymptomatic patients.[14]

In addition to the direct impact of COVID-19 on pregnancy outcomes, there is evidence that the pandemic and its effects on healthcare systems have had adverse effects on pregnancy outcomes, even among those not infected with SARS-CoV-2. In a global systematic review, increases in stillbirths and maternal deaths, declines in maternal mental health (as measured by mean Edinburgh Postnatal Depression Scale scores), and an increased rate of ruptured ectopic pregnancies representing a delay in appropriate care were observed during the pandemic compared to before the pandemic.[34] This deterioration in several maternal health measures,, which was more pronounced in low-resource compared to high-resource settings, may represent widening disparities and an alarming reversal of recent improvements in maternal and infant health.[35] Paradoxically, an overall decline in preterm birth rates was seen during pandemic

lockdown periods in some[36-40] but not all[41,42] high-resource settings, largely due to reductions in extreme prematurity. Although these trends could represent a shift in deliveries from liveborn premature infants to stillborn infants, alternatively, these may represent true improvements in birth outcomes in some settings. Since our efforts over many decades to prevent preterm birth have been largely unsuccessful, these findings are intriguing and could potentially hold clues to long-standing challenges to preventing preterm births.

Management of COVID-19 Infection in Pregnancy

In general, the clinical management of pregnant person with COVID-19 is similar to non-pregnant persons, and effective treatments should not be withheld based on pregnancy status.[43] For example, antiviral therapy with remdesivir should not withheld if otherwise indicated even with limited albeit reassuring safety data.[44] Several types of monoclonal antibodies have been authorized for treatment of symptomatic COVID-19 patients who are at high risk for progressing to severe COVID-19 and/or hospitalization. Since pregnancy is included as a risk for clinical progression, pregnant patients are eligible to receive outpatient monoclonal antibodies under Emergency Use Authorization. Dexamethasone is recommended for patients with COVID-19 who are mechanically ventilated or require supplemental oxygen including pregnant women. Prophylactic anticoagulation is recommended for hospitalized patients with COVID and this includes pregnant patients. Although other therapeutic options for COVID-19 are being evaluated, many clinical trials for novel therapeutic agents exclude pregnant persons.[44,45]

Although clinical algorithms for treating COVID are similar in pregnant and nonpregnant persons, there are some important differences. Oxygen saturation (SpO2) in pregnancy should be maintained at 95% or greater on room air so the threshold for admitting pregnant patients may

be lower than for nonpregnant patients. In addition, scoring systems to assess clinical deterioration and need for admission to an intensive care unit have not been well validated in pregnant persons. Therefore, algorithms specifically tailored for pregnancy may be helpful. Prone positioning has been shown to be of benefit for some COVID patients such as those who are mechanically ventilated; the prone position is safe in pregnancy and can safely be achieved with some possible modification such as positioning in the left lateral decubitus position.[45]

In general, COVID is not an indication for delivery and should not alter the timing nor mode of delivery. However, in some cases where delivery is not medically indicated, delivery may be delayed until the mother tests negative for COVID to decrease the likelihood of transmission to the neonate.[43]

Clinical guidelines for the management of pregnant patients with COVID have been developed by the NIH and the Society for Maternal and Fetal Medicine (SMFM) are regularly updated and provide an excellent source for up-to-date information. [44,45]

COVID-19 Vaccination in Pregnant and Lactating Persons

Three COVID-19 vaccines are currently available: two mRNA vaccines (Pfizer-BioNTech and Moderna) and one adenoviral vector vaccine (Johnson & Johnson-Janssen) (Table). CDC specifies that any of the currently authorized vaccines can be administered to pregnant or lactating persons, with no preference for vaccine type.[46] The American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal and Fetal Medicine (SMFM) and CDC strongly recommend that pregnant and lactating persons be vaccinated. ACOG further specifies pregnant persons should be encouraged to talk to their obstetric healthcare provider about their vaccination plan and discuss any questions they have; however, this should not be a

231 requirement for vaccination because it could serve as a barrier. Pregnant patients who decline
232 vaccination should be reoffered the vaccine and reminded about the importance of continuing
233 other prevention measures such as wearing a mask and physical distancing.[43] ACOG guidance
234 also does not state a preference for vaccine type nor for timing of vaccination during
235 pregnancy.[43] In the United Kingdom, the Royal College of Obstetricians & Gynaecologists
236 recommends an mRNA vaccine for pregnant persons because there are more safety data
237 available for the mRNA vaccine compared to the adenoviral vaccines.[47]. This may have
238 implications for countries where only adenoviral vaccines are available. CDC recently reported
239 that among nearly 136,000 pregnant persons who had not completed COVID-19 vaccination
240 before pregnancy, only 16% received ≥1 dose of vaccine and 11% had completed vaccination
241 during pregnancy. COVID-19 vaccination during pregnancy was lowest among persons of Black
242 and Hispanic race-ethnicity and among younger women (aged 18-24 years of age). Pregnant
243 persons were less likely to be vaccinated than nonpregnant women of reproductive age.[48]

244 Although safety data in pregnancy were fairly limited when these vaccines were first
245 available in the United States, data are rapidly accumulating. Nearly 150,000pregnant persons
246 have signed up for v-safe, CDC's smart phone-based tool that uses text messaging and web-
247 based surveys to collect information from those who have received a COVID-19 vaccine, and
248 more than 5,000 pregnant persons have enrolled in the v-safe pregnancy registry, which follows
249 pregnant persons and their infants until 3 months after pregnancy completion.[49] In a preliminary
250 analysis of pregnant persons who received an mRNA vaccine, which included 35,691 pregnant
251 persons who registered for v-safe and 3,958 pregnant persons who enrolled in the registry
252 (including 827 with a completed pregnancy), no concerning safety signals were seen. Although
253 there were some small differences, pregnant persons and non-pregnant women had similar

reactogenicity profiles. Compared with nonpregnant women, pregnant persons had slightly higher rates of injection-site pain and slightly lower rates of headache, myalgia, chills, and fever. Among the 827 pregnant persons who had a completed pregnancy reported in the v-safe pregnancy registry, the rates of adverse pregnancy and neonatal outcomes including pregnancy loss, preterm birth, small for gestational age, and congenital anomalies were similar to published background rates; no neonatal deaths were reported.[50] Data from the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system administered by the CDC and FDA that collects information about adverse events that occur after administration of a vaccine that may or may not be associated with vaccine administration, are also reassuring. In the first two months of vaccine administration, 221 adverse pregnancy events were reported to VAERS including 46 spontaneous abortions, similar to what was observed with the 2009 H1N1 inactivated influenza vaccine.[50] However, VAERS data are difficult to interpret, given that the total number of COVID-19 vaccine doses given during pregnancy is unknown. Healthcare providers should report any clinically significant adverse event to VAERS, regardless of whether the vaccine is known to be associated with the event.[51]

Safety data about the Johnson & Johnson-Janssen (adenoviral vector) COVID-19 vaccine are more limited since it was authorized for use later, and far fewer vaccines have been administered. At the time of authorization, data from animal studies and on four pregnant persons who received the COVID-19 vaccine during clinical trials were reassuring, and over 1500 pregnant persons had received an Ebola vaccine using the same adenoviral vector without adverse effects. In materials submitted to the FDA, Johnson & Johnson-Janssen concluded that the vaccine had an "acceptable safety and reactogenicity profile without significant safety issues" and that the available pregnancy data were "not suggestive of pregnancy-related safety

277 concerns".[52] The FDA concluded that data were currently insufficient to make conclusions about
278 the safety of the vaccine in pregnancy.[53] Although no safety signals in pregnancy have been
279 detected, safety data about all three currently available vaccines during pregnancy are limited.
280 Additional information about birth outcomes, particularly among persons vaccinated earlier in
281 pregnancy, are needed.

282 Following the issuance of the Johnson & Johnson-Janssen EUA by FDA, six cases of
283 cerebral venous sinus thrombosis with thrombocytopenia were reported among Johnson &
284 Johnson-Janssen vaccine recipients. Similar cases of thrombosis with thrombocytopenia
285 syndrome (TTS) were reported after vaccination with the Oxford AstraZeneca adenoviral
286 vaccine that is available in multiple countries outside of the U.S.[54] After a 10-day pause in use
287 of the vaccine in the U.S. so that all cases of TTSassociated with vaccine use could be carefully
288 reviewed, an additional nine cases were identified, with most cases in women aged 18-49 years,
289 for a rate of 7.0 cases per million Johnson & Johnson-Janssen COVID-19 vaccine doses given to
290 women in this age group. After careful review of the risks and benefits of COVID-19
291 vaccination, the CDC and FDA reaffirmed use in all persons ≥18 years and issued a warning that
292 rare clotting events might occur after vaccination, particularly among women aged 18-49 years.[55]
293 Clinicians should ensure that women younger than 50 years old are aware of the risk for this rare
294 adverse event and that other COVID-19 vaccines for which this risk has not been seen are
295 available. Although the overall risk of thrombosis is increased during pregnancy and postpartum,
296 the mechanism of TTS is distinct from the pregnancy-associated thrombosis and therefore there
297 is no specific concern for pregnant persons distinct from those who are not pregnant.[43] However,
298 the United Kingdom preferentially recommends mRNA vaccines rather than adenoviral vaccines
299 based on these safety concerns.[47]

In terms of vaccine effectiveness, studies indicate that administration of the mRNA vaccines results in a robust maternal humoral response. Although the antibody response to vaccination among pregnant persons has not been rigorously compared to the response among nonpregnant persons, there is no reason to expect differences. Furthermore, maternal IgG antibodies efficiently cross the placenta resulting in relatively high titers in the fetus.[56-60] However, the degree to which these fetal antibody titers correlate with infant protection from SARS-CoV-2 infection is unknown.

Regarding vaccinating lactating persons, there are no known or theoretical risks of vaccination.. In general, there are no restrictions to vaccination of lactating persons and even live viral vaccines such as measles-mumps-rubella (MMR) vaccines, which are contraindicated during pregnancy, are routinely given to unvaccinated persons postpartum. High titers of vaccine-induced antibodies against SARS-CoV-2 have been found in breastmilk.[57,58] However, whether this correlates with protection of the breastfed infant is unknown.

Several myths and misconceptions have arisen about COVID-19 vaccines, and clinicians need to be prepared to respond to questions regarding these patient concerns. Women should be reassured that there is no evidence that COVID-19 vaccines affect fertility and that even in COVID-19 vaccine clinical trials, from which pregnant persons were excluded, several pregnancies occurred.[61] Patients should also be aware that these vaccines cannot cause COVID-19, since none of them contain live virus, that COVID-19 vaccines do not interact with or alter genetic material, and that vaccines do not contain any controversial substances (e.g., fetal cells or tracking devices). CDC recommends that clinicians listen and respond to patient concerns regarding COVID-19 vaccines with empathy.[62] As with other vaccines, discussion with a clinician is important; in a recent Kaiser Family Foundation poll, nearly 80% of respondents

reported that they would be most likely to turn to their healthcare provider when deciding whether to get a COVID-19 vaccine.[63]

Conclusions

Since reports of the first cases of COVID-19 in late 2019, much has been learned about the effects of SARS-CoV-2 infection during pregnancy; however, many questions remain. Pregnancy increases the risk of severe disease associated with COVID-19, but whether pregnant persons are more susceptible to infection is unknown. Intrauterine transmission of SARS-CoV-2 appears to be rare, possibly related to low levels of SARS-CoV-2 viremia and decreased co-expression of ACE2 and TMPRSS2 needed for SARS-CoV-2 entry into cells in the placenta. Adverse pregnancy and neonatal outcomes are more common among persons infected with SARS-CoV-2 during pregnancy, especially among those with severe disease. Although pregnant and lactating persons were excluded from the initial clinical trials that led to authorization of three COVID-19 vaccines in the United States, no concerns have arisen about safety, despite large numbers of pregnant and lactating persons vaccinated. Despite reports of rare clotting events in vaccinated persons, there is not a particular concern for those with a prothrombotic state, including pregnancy. In addition, available data suggest that vaccination during pregnancy is associated with transmission of SARS-CoV02 antibodies to the fetus. Vaccination of lactating persons is associated with high levels of SARS-CoV-2 antibodies in the breast milk; however, the level of protection to the infant provided by transplacental antibodies and those found in breastmilk is unknown. Data on vaccine coverage suggests that pregnant persons are less likely to receive a COVID-19 vaccine, despite their increased risk for severe disease and risk for adverse pregnancy and neonatal outcomes if infected.

Most experts believe that SARS-CoV-2 is likely to become endemic.[64] Thus, continued collection of data on the effects of SARS-CoV-2 infection during pregnancy as well as the effects of COVID-19 vaccines is needed. In addition, given the increasing connectedness of the world's population, climate change, and increasing encroachment of human populations on wildlife habitats, emergence of another infection with global effects is likely.[65] Therefore, it is essential that we can maximize the lessons learned from the COVID-19 pandemic so these can be applied to improve our planning for and response to emerging infections in the future.

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Table: Safety Data during Pregnancy on COVID-19 Vaccines Authorized for Use in the United States

Vaccine	Technology	Number of doses	Ages	Efficacy based on randomized clinical trials	Developmental and reproductive toxicity studies in animals	Safety signals in general population (reporting rate of adverse outcomes and population with highest rate)	Published safety data on pregnant persons
Pfizer-BioNtech mRNA vaccine (BNT162b2)	mRNA – encodes stabilized spike, lipid nanoparticle	Two doses, 3 weeks apart	>=12 years	95% against symptomatic COVID-19	No safety concerns – rats given vaccine before mating and in pregnancy – no effects on female mating performance, fertility, embryofetal or postnatal survival, growth, physical or neurofunctional development (ACOG, 2020)	Myocarditis – more often after 2nd dose – Reporting rate: 3.5 cases per 1,000,000 second doses; Highest rate population: males aged 18–29 years; (mRNA vaccine analyzed together) (Rosenblum et al., 2021)	No evidence of obvious safety signals among 3598 pregnant participants in v-safe pregnancy registry who received mRNA vaccine, 827 with completed pregnancies (mRNA vaccines analyzed together) – (Shimabukuro et al., 2021); No evidence of adverse outcomes among 390 pregnant persons who received the Pfizer vaccine (Bookstein Peretz et al., 2021); No evidence of adverse perinatal outcomes among pregnant persons who received Pfizer (n=110), Moderna (n=18), or Oxford

							Astra Zeneca (n=13) (vaccines analyzed together (Blakeway et al., 2021); No evidence of increased risk of adverse perinatal outcomes among 13 pregnant persons who received mRNA vaccine; type not specified. (Gray et al 2021); No concerning trends in perinatal outcome among 65 pregnant persons who received Pfizer vaccine (Trostle et al 2021). *+
Moderna mRNA-1273 vaccine	mRNA, encodes stabilized spike, lipid nanoparticle	Two doses, 28 days apart	>=18 years	94.1% against symptomatic COVID-19	No safety concerns – rats were given vaccine before mating and during pregnancy – no adverse effects on female fertility, embryofetal or postnatal survival, growth, or	Myocarditis – more often after second dose - 3.5 cases per 1,000,000 second doses – highest rate among males aged 18–29 years (mRNA vaccine analyzed together) (Rosenblum et al., 2021)	No evidence of obvious safety signals among 3598 pregnant participants in v-safe pregnancy registry who received mRNA vaccine, 827 with completed pregnancies (mRNA vaccines analyzed together) – (Shimabukuro et al., 2021); No evidence of adverse perinatal

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Janssen Biotech, Inc. (Johnson & Johnson) Ad26.COV2.S vaccine:	Replication-incompetent human adenovirus type 26 vector-stabilized spike	One dose	>=18 years	66.1% against moderate to severe-critical COVID-19; 85.4% against severe-critical COVID-19	No safety concerns – female rabbits were given vaccine before mating and during pregnancy – no vaccine-related	Thrombosis with thrombyocytopenia syndrome (TTS) – 3 cases per 1,000,000 doses administered – highest rate in females aged 30-49 years (Rosenblum et al., 2021)	We are not aware of published data on use of Janssen vaccine during pregnancy. No adverse pregnancy-related outcomes in clinical trials that used the same vaccine platform, including

					adverse effects on female fertility, embryo-fetal or postnatal development up to postnatal day 28 (ACOG, 2020)	Guillain-Barre syndrome –7.8 cases per 1,000,000 doses administered – highest rate in males aged 50-64 years (Rosenblum et al., 2021)	large Ebola vaccination trial. [+]

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Footnotes:

* A preprint publication (not yet peer reviewed) reporting updated data from v-safe confirms that receipt of mRNA vaccine preconception or during pregnancy is not associated with an increased risk of spontaneous abortion (Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA COVID-19 vaccines preconception and during pregnancy and risk of self-reported spontaneous abortions, CDC v-safe COVID-19 Vaccine Pregnancy Registry 2020-21. Research Square 2021).

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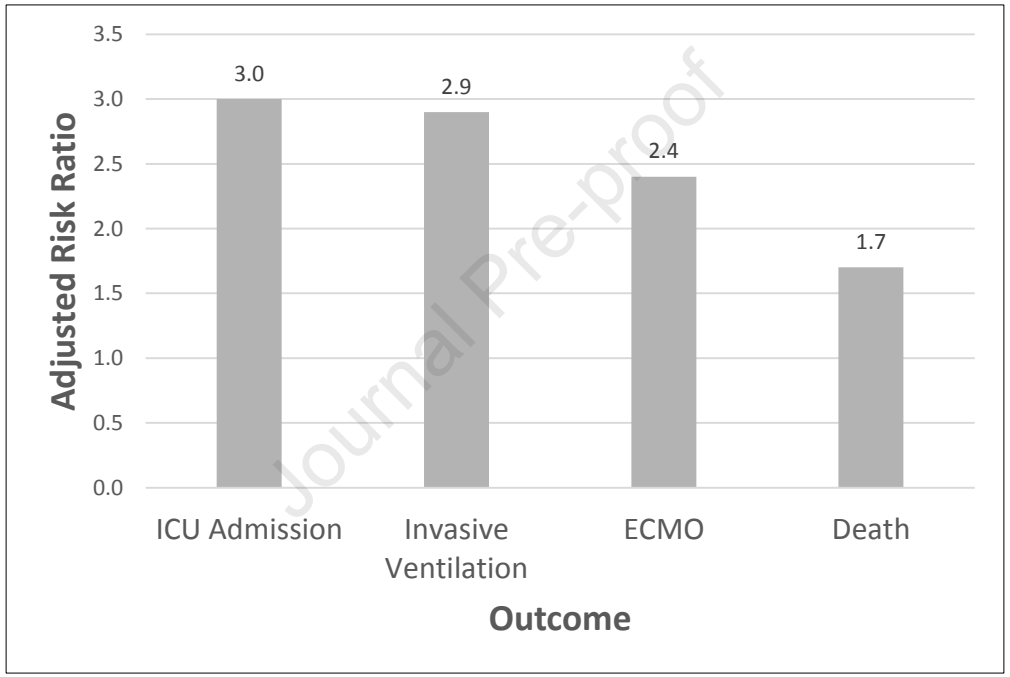
Figure. Risk of severe COVID-19 –associated outcomes among pregnant persons compared with non-pregnant women adjusted by age, race/ethnicity, and underlying medical conditions.



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ICU=intensive care unit
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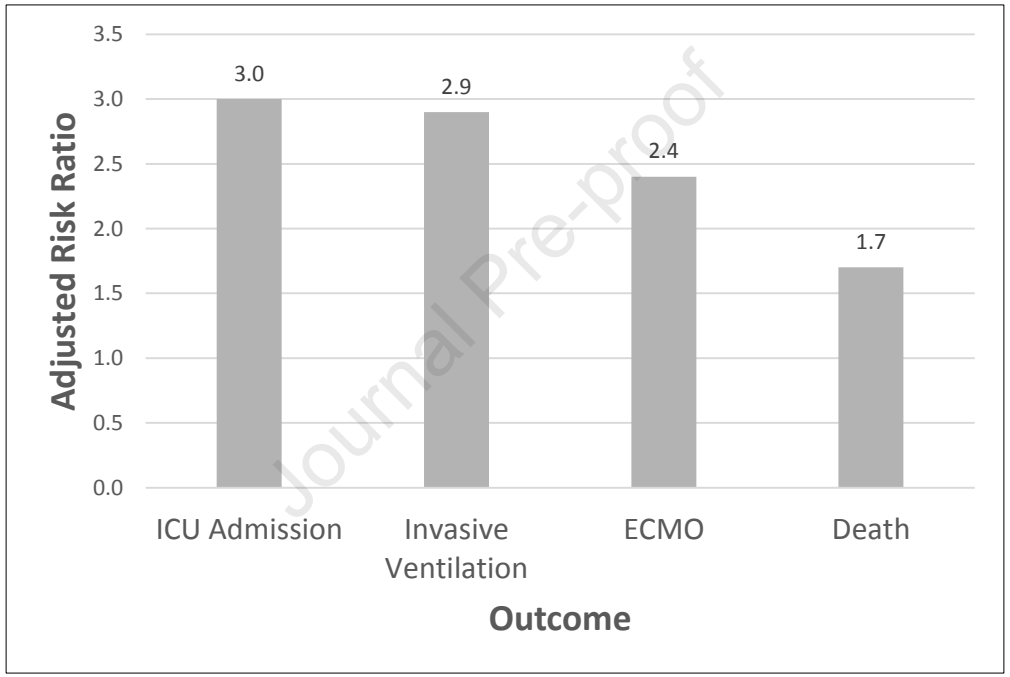

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