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The impact of maternal SARS-CoV-2 infection and COVID-19 vaccination on maternal-fetal outcomes

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ABSTRACT

The rapidly evolving COVID-19 pandemic has resulted in an upsurge of scientific productivity to help address the global health crisis. One area of active research is the impact of COVID-19 on pregnancy. Here, we provide an epidemiological overview about what is known about the effects of maternal SARS-CoV-2 infection and COVID-19 vaccination on maternal-fetal outcomes, and identify gaps in knowledge. Pregnant people are at increased risk for severe COVID-19, and maternal SARS-CoV-2 infection increases the risk of negative maternal-fetal outcomes. Despite this elevated risk, there have been high rates of vaccine hesitancy, heightened by the initial lack of safety and efficacy data for COVID-19 vaccination in pregnancy. In response, retrospective cohort studies were performed to examine the impact of COVID-19 vaccination during pregnancy. Here, we report the vaccine's efficacy during pregnancy and its impact on maternal-fetal outcomes, as well as an overview of initial studies on booster shots in pregnancy. We found that pregnant people are at risk for more severe COVID-19 outcomes, maternal SARS-CoV-2 infection is associated with worse birth outcomes, COVID-19 vaccine hesitancy remains prevalent in the pregnant population, and COVID-19 vaccination and boosters promote better maternal-fetal outcomes. The results should help reduce vaccine hesitancy by alleviating concerns about the safety and efficacy of administering the COVID-19 vaccine during pregnancy. Overall, this review provides an introduction to COVID-19 during pregnancy. It is expected to help consolidate current knowledge, accelerate research of COVID-19 during pregnancy and inform clinical, policy, and research decisions regarding COVID-19 vaccination in pregnant people.

1. Introduction

The COVID-19 pandemic has been evolving rapidly. Scientific research into the changing nature of COVID-19 and its impact on health outcomes has often lagged behind in the pregnant population. This lack of information has led to fear and distress in pregnant people, and contributed to vaccine hesitancy. Two major areas of concern are the impact of SARS-CoV-2 infection and COVID-19 vaccination on maternal-fetal outcomes. We therefore performed a literature review focusing on large retrospective cohort studies and concisely report what is currently known about these topics from an epidemiological perspective. It is important to acknowledge that the majority of the large-scale retrospective cohort studies to date on the impact of maternal SARS-CoV-2 infection and COVID-19 vaccination on maternal-fetal outcomes have been conducted in pregnant people in high-income countries. Future studies examining the impact of these exposures on maternal-fetal outcomes should be conducted in middle and lower income countries to verify these results in the context of those populations.

Here, we provide a brief overview of what is known about the impact of maternal SARS-CoV-2 and COVID-19 vaccination on maternal-fetal outcomes. First, we examine the effect of a SARS-CoV-2 infection on maternal health, impact of SARS-CoV-2 variant on infection severity, and then the effect of maternal SARS-CoV-2 infection on birth outcomes. Next, we provide a brief history of recommendations for vaccination against COVID-19 during pregnancy. Then we explore vaccine hesitancy in the pregnant population and the disparity of vaccine uptake in pregnant people by race, ethnicity, age, and socioeconomic status. We then report the impact of COVID-19 vaccination on maternal-fetal outcomes and provide additional information on boosters during pregnancy from initial studies. Altogether, this review summarizes what is known as of August 25, 2022 on the impact of SARS-CoV-2 infection and COVID-19 vaccination during pregnancy.

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2. Methods

We identified studies to include in this review using the following methodology. On August 25, 2022 on PubMed we searched for studies containing keywords "COVID-19" OR "SARS-CoV-2" paired with "pregnancy" AND "retrospective cohort". We then read the titles and abstracts to identify studies investigating either the impact of maternal SARS-CoV-2 infection or COVID-19 vaccination on maternal-fetal outcomes. To be more confident that results in studies were not impacted by small sample size, studies included in this review are limited to those that had at least a hundred people per cohort for the study's primary outcome. In this review we did not include case, descriptive, or meta-analyses studies on the impact of infection or vaccination on maternal-fetal outcomes. To identify cross-sectional studies on vaccine hesitancy we searched for studies including keywords "COVID-19" OR "SARS-CoV-2" paired with "pregnancy", "vaccine", "hesitancy", AND "cross-sectional". Vaccine hesitancy was defined as being unsure or resistant to receiving the COVID-19 vaccine. We limited vaccine hesitancy studies to descriptive or retrospective cohort studies, but did not limit study inclusion based on the number of participants. We also retrieved additional relevant studies from references or major landmark studies on COVID-19 that were referenced by the Center for Disease Control and Prevention (CDC) to support their recommendations to the public regarding COVID-19 and pregnancy.

All studies included in this review are limited to those in English and those to which the authors had access to the full text of the manuscript. The studies were screened by abstract and title for meeting the review criteria of inclusion. Full articles were retrieved and reviewed to evaluate their relevance to this review in cases in the event of uncertainty after reading the abstract. One researcher then screened the full text of all studies and collated their results. They then summarized and interpreted the results in this review, which was reviewed and approved by all authors.

For information regarding the maternal-fetal outcomes following a SARS-CoV-2 infection the following information was manually extracted from each study: first author and year of publication, study setting, sample size of those with COVID-19, sample size of those without COVID-19, the fold change in the rate of the outcome of those with COVID-19 versus those without COVID-19, and when applicable the p-value. The fold change was manually calculated from the proportion of people with the outcome between the two groups. If the raw numbers of people with a particular outcome were not available, then the study was not included in the table summaries. In cases in which propensity score matched cohorts were provided, they were used to calculate the fold change. The p-value (calculated by chi square or fisher's exact test) provided is the one from the study themselves and was listed as "NA" in cases in which it was not statistically calculated by the authors, typically due to providing crude and adjusted hazard risk ratios, odds ratios, or relative risk ratios instead. In addition, the following about vaccine hesitancy was manually retrieved: first author and year of publication, study setting, study time period, study sample size, and raw count and proportion of people that were reported as vaccine hesitant in the study. The relevant data was extracted and organized in an Excel spreadsheet.

3. Maternal SARS-CoV-2 infection impact on maternal-fetal outcomes

It became clear early on in the COVID-19 pandemic that pregnant people are at elevated risk of harm from SARS-CoV-2 infection compared to non-pregnant women of reproductive age.[1–9] People with a SARS-CoV-2 infection during pregnancy also have worse maternal outcomes than those that do not [6,10–16]. SARS-CoV-2 infection and related complications has also disproportionately impacted minority populations and people with lower socioeconomic status [11,16–19]. In addition, SARS-CoV-2 variants have had significantly different impacts on COVID-19 severity in pregnant people [7, 19–24]. Maternal SARS-CoV-2 infection also leads to increased risk of negative birth outcomes including preterm birth, stillbirth, small for gestational age (SGA; <10th fetal growth percentile at delivery), and decreased birth weight [7,11,13,16,18,19,25]. Further research is needed to elucidate methods to decrease the risk of adverse maternal-fetal outcomes following a maternal SARS-CoV-2 infection.

3.1. SARS-CoV-2 infection severity during pregnancy

Pregnancy increases the risk of having more severe outcomes from COVID-19 [1–9]. Pregnant people have 1.8–5.4 fold higher hospitalization rates [1,3,4,6,7,9], and 1.3–5.5 fold higher ICU admission rates (Table 1) [1,2,5–7]. Results are more mixed on the relative risk of severe COVID-19 (0.8–2.0 fold difference) [8,26], mechanical ventilation (0.4–2.7 fold difference) [1–3,5,6], and death (0.1–13.6) [1–6] during COVID-19 for pregnant people compared to non-pregnant women of reproductive age (Table 1). Mechanical ventilation and death remain rare, which may explain discrepancies in reporting on the relative risk in pregnant people compared to non-pregnant people. One study noted that half of pregnant people with COVID-19 were admitted during labor and delivery encounters and postulated that hospitalization is not necessarily an indicator of severe COVID-19 in pregnant people [3]. After excluding labor and delivery encounters, pregnant people had a 2.2–2.3 fold elevated rate of hospitalization compared to non-pregnant women [3,9]. However, pregnant people had similar rates of mechanical ventilation and death as non-pregnant women.[3] Overall, this indicates that pregnancy should be considered similar to other pre-existing conditions, which elevate a person's risk for more severe outcomes from COVID-19, although the overall risk remains low in this population.

In addition, people with COVID-19 during pregnancy universally had more severe outcomes than those that did not [6,10–16]. Pregnant people that had a COVID-19 during pregnancy have a 2.7–4.6 fold increased risk for a thrombotic event compared to pregnant people that did not have an infection (Table 2).[11,16] They also had a 1.7–13.5 fold increased rate of ICU admission [6,10–16] and a 2.8–25.4 fold increased risk of mechanical ventilation (Table 2) [6,10,11,16]. Maternal age, higher BMI, smoking, or having chronic comorbidities was positively associated with COVID-19-related ICU admission.[27] Moreover, a maternal SARS-CoV-2 infection substantially increases the risk of maternal mortality with people with COVID-19 dying at 3.7–22.3 times the rate of people without COVID-19 during pregnancy (Table 2) [6, 10–13]. Furthermore, women with high-risk pregnancies were at elevated risk for more severe COVID-19 outcomes [28]. While the overall risk for severe COVID-19 outcomes remains low, the high change in relative risk makes it important that pregnant people take steps to decrease their risk of contracting COVID-19 including receiving the COVID-19 vaccine and adapting habits to decrease the risk of exposure. One such option to decrease the risk of severe COVID-19 outcomes is to administer monoclonal antibodies, which has been shown to decrease the risk for COVID-19-related hospital admission when administered to unvaccinated pregnant people with mild or moderate COVID-19 [29]. Studies examining pharmacological interventions in pregnant people remain rare and typically have small sample sizes. More of these studies are needed to enable effective care of pregnant people with COVID-19.

Studies have also considered the effect of COVID-19 on the development of common pregnancy-related conditions including gestational diabetes, gestational hypertension, and preeclampsia, but the impact of infection on developing these conditions remains unclear [7,11,13,15, 16,18,30,31]. Three studies report a 1.2–1.5 fold increase in gestational diabetes in people with a maternal SARS-CoV-2 infection [11,16,31], but two studies report no change in rates (Table 3) [15,18]. The results for gestational hypertension are even more mixed, with two studies noting a decrease in rate (0.8 fold difference) [11,16] , two studies recording a 1.5–1.8 fold increase [13,31], and two studies reporting no change in rate (Table 3) [18,30]. In addition, two studies show similar rates of gestational hypertension and gestational diabetes in pregnant

Table 1
COVID-19-related outcomes in pregnant people and non-pregnant women of reproductive age.

Outcome	Study	Study Setting	With COVID-19 (n)	Without COVID-19 (n)	Fold Change (COVID-19 vs no COVID-19)	p-value
Death	Ellington et al. 2020	US	8,207	83,205	1.0	NA
	Hsu et al. 2022	US	18,089	3,042	0.1	$p < 0.05$
	Lokken et al. 2021	Washington, US	240	34,902	13.6	NA
	Pineles et al. 2022	US	2,250	2,250 matched (21,503 total)	0.4	NA
	Ríos-Silva et al. 2020	Mexico	448	17,942	0.8	$p = 0.5$
	Zambrano et al. 2020	US	23,434	386,028	1.3	NA
Hospitilization	Ellington et al. 2020	US	8,207	83,205	5.4	NA
	Hsu et al. 2022	US	18,089	3,042	3.6	$p < 0.001$
	Lokken et al. 2021	Washington, US	240	34,902	3.5	NA
	Magnus et al. 2022	Norway and Sweden	708	16,364	4.2	NA
	McClymont et al. 2022	Canada	6,012	9,196	2.7	NA
	Ríos-Silva et al. 2020	Mexico	448	17,942	1.8	$p < 0.001$
ICU Admission	Ellington et al. 2020	US	8,207	83,205	1.7	NA
	Pineles et al. 2022	US	2,250	2250 matched (21,503 total)	1.3	NA
	McClymont et al. 2022	Canada	6,012	9,196	5.5	NA
	Ríos-Silva et al. 2020	Mexico	448	17,942	1.4	$p = 0.2$
	Zambrano et al. 2020	US	23,434	386,028	2.7	NA
Mechanical Ventilation	Ellington et al. 2020	US	8,207	83,205	1.7	NA
	Hsu et al. 2022	US	18,089	3,042	0.4	$p = 0.45$
	Pineles et al. 2022	US	2250	2,250 matched (21,503 total)	1.1	NA
	Ríos-Silva et al. 2020	Mexico	448	17,942	0.9	$p = 0.7$
	Zambrano et al. 2020	US	23,434	386,028	2.7	NA
Severe COVID-19	Ahn et al. 2022	South Korea	705	57,323	0.8	$p = 0.06$
	Shoji et al. 2022	Japan	187 matched (254 total)	935 matched (3,752 total)	2.0	$p < 0.05$

Table 2
Maternal outcomes in pregnant people with and without COVID-19.

Outcome	Study	Study Setting	With COVID-19 (n)	Without COVID-19 (n)	Fold Change (COVID-19 vs no COVID-19)	p-value
Death	Chinn et al. 2021	US	18,715	850,364	15.4	$p < 0.001$
	Ko et al. 2021	US	6,650	482,921	20.7	NA
	Ríos-Silva et al. 2020	Mexico	448	1,216	3.7	$p < 0.01$
	Simon et al. 2022	France	2,927	507,460	6.0	$p < 0.01$
	Villar et al. 2021	Multinational (18 countries)	706	1,424	22.2	NA
ICU Admission	Chinn et al. 2021	US	18,715	850,364	5.6	$p < 0.001$
	Gulersen et al. 2022	New York, US	1,653	20,785	3.6	NA
	Jering et al. 2021	US	6,380	400,066	7.6	$p < 0.001$
	Ko et al. 2021	US	6,650	482,921	2.9	NA
	Metz et al. 2021	US	2,352	11,752	3.1	NA
	Ríos-Silva et al. 2020	Mexico	448	1,216	1.7	$p = 0.1$
	Simon et al. 2022	France	2,927	507,460	13.5	$p < 0.01$
	Villar et al. 2021	Multinational (18 countries)	706	1,424	5.2	NA
Mechanical Venhilation	Chinn et al. 2021	US	18,715	850,364	14.8	$p < 0.001$
	Jering et al. 2021	US	6,380	400,066	25.4	$p < 0.001$
	Ko et al. 2021	US	6,650	482,921	13.3	NA
	Ríos-Silva et al. 2020	Mexico	448	1,216	2.8	$p < 0.05$
Thrombotic Event	Jering et al. 2021	US	6,380	400,066	4.6	$p < 0.001$
	Ko et al. 2021	US	6,650	482,921	2.7	NA

Table 3
Rates of pregnancy-related disorders in people with or without COVID-19.

Outcome	Study	Study Setting	With COVID-19 (n)	Without COVID-19 (n)	Fold Change (COVID-19 vs no COVID-19)	p-value
Gestational Diabetes	Epelboin et al. 2021	France	874	243,771	1.3	$p < 0.001$
	Gulersen et al. 2022	New York, US	1,653	20,785	0.9	$p = 0.66$
	Jering et al. 2021	US	6,380	400,066	1.5	$p < 0.05$
	Ko et al. 2021	US	6,650	482,921	1.2	$p < 0.0001$
	Piekos et al. 2022	Western US	882	17,453 (889 matched)	0.9	$p = 0.47$
Gestational Hypertension	Epelboin et al. 2021	France	874	243,771	1.8	$p < 0.001$
	Jering et al. 2021	US	6,380	400,066	0.8	$p < 0.001$
	Ko et al. 2021	US	6,650	482,921	0.8	$p < 0.0001$
	Hughes et al. 2021	US	402	11,705	1.0	NA
	Piekos et al. 2022	Western US	882	17,453 (889 matched)	0.8	$p = 0.33$
	Villar et al. 2021	Multinational (18 countries)	706	1,424	1.5	NA
Preeclampsia	Jering et al. 2021	US	6,380	400,066	1.3	$p < 0.001$
	Ko et al. 2021	US	6,650	482,921	1.4	$p < 0.0001$
	Hughes et al. 2021	US	402	11,705	1.1	NA
	McClymont et al. 2022	Canada	1,260	428,813	0.9	$p = 0.53$
	Piekos et al. 2022	Western US	882	17,453 (889 matched)	1.0	$p = 0.66$
	Villar et al. 2021	Multinational (18 countries)	706	1,424	1.9	NA

people with symptomatic versus asymptomatic infections.[32,33] Finally, three studies report a 1.3–1.9 fold increase in the rate of pre-eclampsia following COVID-19 [11,13,16], whereas three report no change in rate (Table 3) [7,18,30]. Although the impact of COVID-19 on common pregnancy-related disorders remains unclear, any affect appears to be small at most. Differences in these results could be attributed to underlying cofactors. More research is needed to elucidate the impact of maternal COVID-19 and identify which subpopulation of pregnant people will be at highest risk for developing these conditions.

From early on in the pandemic it became clear that COVID-19 disproportionately impacted racial minority and low-income communities [34,35]. This pattern is also observed in pregnant people. People who are Hispanic or identify as a race other than White or Asian had higher rates of maternal SARS-CoV-2 infection [10,11,15,16,18,30,36–39]. In addition, people with COVID-19 during pregnancy tended to be younger, have higher BMI, have pre-existing conditions, have lower educational attainment, and have lower socioeconomic status [10,11,15,16,18,30,38,39]. These disparities are especially concerning given that people that are younger, of lower socioeconomic status, Hispanic ethnicity, or reported race other than Asian or White are less likely to be vaccinated [19,20,40–45]. Greater effort should be made to support COVID-19 vaccination for members of these communities and ensure that they have access to enhanced prenatal care to reduce the impact of these disparities.

3.2. Effect of SARS-CoV-2 variant on COVID-19 severity

From wild-type through Alpha (B.1.1.7), Delta (B.1.617.2) and Omicron (B.1.1.529), each variant has become increasingly transmissible [46–48]. Delta was more likely to cause more severe infection than either Alpha or Omicron [46–48]. This variability in variant transmissibility and disease severity led to differences in the number of cases and hospitalizations during each variant wave, and these trends hold true in the pregnant population [7,19–21,49]. There were lower COVID-19 case numbers in pregnant people during Alpha dominance in the US and UK compared to the wild-type dominance [19,21,22]. The lower case numbers during the Alpha wave may have been impacted due to the onset of vaccination programs in the US and UK shortly before the start of the Alpha wave in these countries. There was a noticeable increase in cases following Delta achieving dominance [19,21,23,49] with one report of 3.1 greater odds of becoming infected during the Delta wave [23], although cases were primarily observed in unvaccinated pregnant people [20,24]. There were substantially higher number of cases during the Omicron wave compared to the Delta wave (OR: 10.09) [23] with a spike in cases observed in both vaccinated and unvaccinated individuals [20,22,23,49].

There were increased rates of hospitalization, supplemental oxygen use, and ICU admission during Alpha dominance compared to wild-type dominance [21], which increased further during Delta dominance [7,21,50]. Pregnant people likely infected with Delta had 1.8–2.9 fold increased odds of developing severe illness compared to previous variants, whereas those likely infected with Omicron had 0.1–0.2 the odds of developing a severe illness compared to those with Delta [23,49]. There was an overall increase in severe maternal morbidities associated with SARS-CoV-2 infections during Delta dominance, which decreased substantially during Omicron dominance [51]. Maternal mortality was also substantially higher (3.5 fold increase) during Delta dominance [22,50] as well as stillbirth rates (2.7 fold increase) following a maternal SARS-CoV-2 infection compared to a pre-Delta infection [25,50]. In addition, pregnant people were admitted to the ICU, mechanical ventilation, and died at higher rates during the second wave of COVID-19 (variant not specified) in Brazil [52]. Overall, there are relatively few large population cohort studies that examine the effects of different variants on maternal-fetal outcomes. Given the diversity of clinical outcomes between variants it may be important in future studies to consider the variant of infection a feature when examining and understanding relative risk of maternal-fetal outcomes following a maternal COIVD-19 infection.

3.3. Effect of maternal SARS-CoV-2 infection on fetal outcomes

From the early days of the pandemic there were concerns that COVID-19 during pregnancy may affect the developing fetus and impact birth outcomes. The majority of studies report between a 1.2 and 2.0 fold increased rate of preterm birth following a maternal SARS-CoV-2 infection (Table 4) [7,10–14,16,18,19,30,31,33,36,38,53]. Multiple

Table 4
Birth outcomes in people with or without COVID-19.

Outcome	Study	Study Setting	With COVID-19 (n)	Without COVID-19 (n)	Fold Change (COVID-19 vs no COVID-19)	p-value
Neonatal Death	Badr et al. 2021	Europe	338	10,370	0.4	$p < 0.001$
	Hughes et al. 2021	US	402	11,705	2.4	NA
	Metz et al. 2022	US	2,352	11,752	1.4	NA
NICU Admission	Ahn et al. 2022	South Korea	705	657,705	2.4	$p < 0.0001$
	Badr et al. 2021	Europe	338	10,370	1.7	$p < 0.001$
	Doyle et al. 2022	Florida, US	13,178	224,865	1.2	NA
Perinatal Death	Doyle et al. 2022	Florida, US	13,178	224,865	0.7	NA
	Stock et al. 2022	Scotland, UK	2,364	77,470	4.0	NA
Preterm Birth	Ahn et al. 2022	South Korea	705	657,705	0.7	$p < 0.01$
	Chinn et al. 2021	US	18,715	850,364	1.4	$p < 0.001$
	Dileep et al. 2022	US	1,261	30,289	1.5	$p < 0.001$
	Doyle et al. 2022	Florida, US	13,178	224,865	1.1	NA
	Edlow et al. 2022	Massachusetts, US	222	7,550	1.7	$p < 0.01$
	Epelboin et al. 2021	France	874	243,771	2.0	$p < 0.001$
	Fallach et al. 2022	Israel	2,743	2,743	1.2	$p = 0.15$
	Hughes et al. 2021	US	402	11,705	1.4	NA
	Jering et al. 2021	US	6,380	400,066	1.3	$p < 0.001$
	Karasek et al. 2021	California, US	5,089	146,144	1.4	NA
	Ko et al. 2021	US	6,650	482,921	1.3	NA
	McClymont et al. 2022	Canada	5,746	419,937	1.6	$p < 0.001$
	Metz et al. 2022	US	2,352	11,752	1.3	NA
	Simon et al. 2022	France	2,927	507,460	1.6	$p < 0.01$
	Stock et al. 2022	Scotland, UK	2,364	77,209	1.3	NA
	Villar et al. 2021	Multinational (18 countries)	706	1,424	1.7	NA
Stillbirth	DeSisto et al. 2021	US	21,653	1227,981	2.2	NA
	Doyle et al. 2022	Florida, US	13,178	224,865	0.9	NA
	Hughes et al. 2021	US	402	11,705	1.7	NA
	Jering et al. 2021	US	6,380	400,066	1.7	$p < 0.01$
	Ko et al. 2021	US	6,650	482,921	1.4	NA
	McClymont et al. 2022	Canada	5,743	443,184	0.7	$p = 0.07$
	Metz et al. 2022	US	2,352	11,752	0.7	NA
	Piekos et al. 2022	Western US	882	889 matched (17,453 total)	7.0	$p < 0.05$
Small for Gestational Age (SGA)	Badr et al. 2021	Europe	338	10,370	0.9	$p < 0.001$
	Fallach et al. 2022	Israel	2,743	2,743	1.0	$p = 0.67$
	Hughes et al. 2021	US	402	11,705	1.1	NA
	Piekos et al. 2022	Western US	882	889 matched (17,453 total)	1.3	$p < 0.05$
	Simon et al. 2022	France	2,927	507,460	1.0	$p = 0.71$
	Villar et al. 2021	Multinational (18 countries)	706	1,424	1.1	NA

studies report an increased risk of premature birth even after adjusting for common cofactors [11,12,14,18,31,37,53,54]. Preterm birth is also significantly more likely following COVID-19 in a high-risk pregnancy compared to an infection in a low-risk pregnancy [28]. In addition, several of these studies considered preterm birth in the context of infection severity with mixed reports on how COVID-19 severity impacted preterm birth risk. Multiple studies report an increased risk of preterm birth following a maternal SARS-CoV-2 infection regardless of infection severity, even in the case of asymptomatic infections [7,13,18,33]. These studies examined people who had COVID-19 during pregnancy, including infections that were resolved by the time of labor and delivery. However, several studies reported that although asymptomatic COVID-19 is also associated with increased risk of preterm birth, people with symptomatic or severe/critical COVID-19 have an even higher risk of preterm birth than people with asymptomatic or mild COVID-19 [4,14,53,55–58]. Most other perinatal outcomes were unaffected by infection severity [14,56], although one study suggests that having severe COVID-19 at delivery increases the risk for adverse birth outcomes.[4] Overall, the bigger driver behind the increased risk of adverse perinatal outcomes appears to be the maternal SARS-CoV-2 infection itself rather than infection severity.

Other common birth outcomes examined in the context of a maternal SARS-CoV-2 infection included birth weight, SGA, NICU admission, neonatal death, perinatal mortality, and stillbirth. Babies born to people with COVID-19 during pregnancy weighed significantly less at delivery [12,13,18,38,54,59]. There were mixed reports about whether COVID-19 during pregnancy impacted the relative risk for SGA with one study reporting a 1.3 fold increase,[18] one study recording a 0.9 fold decrease [59], and four noting no change (Table 4) [12,13,30,54]. Babies born to mothers with COVID-19 during pregnancy were also 1.2–2.4 fold more likely to be admitted to the NICU (Table 4) [26,37,59]. Most studies report increased risk for neonatal death, perinatal death, or stillbirth following a maternal SARS-CoV-2 infection, however there are mixed results (Table 4) [7,11,13,14,16,18,19,25,26,30,37,59]. Two studies report a 1.4–2.4 fold increase in neonatal death,[14,30], whereas one study notes a 0.4 fold decrease following a maternal SARS-CoV-2 infection [59]. In addition, Stock et al. reported a 4.0 fold increase in perinatal death following a maternal SARS-CoV-2 infection [19] whereas Doyle et al. notes no change [37]. Finally, five studies report 1.4–7.0 fold increase in stillbirth in people with COVID-19 during pregnancy [11,16,20,25,30] and three studies record no change [7,14,37]. Overall, it appears that COVID-19 during pregnancy negatively affects fetal and neonatal survival. It also increases the risk for other adverse outcomes as a whole.

Differences in the observations of the impact of a maternal SARS-CoV-2 infection on birth outcomes may reflect differences in patient

population, data types, and study designs, as well as the rarity of the events such as stillbirth. Also, some of the differences observed may be explained by cofactors and only some of the studies took any into account during their analyses. Despite these limitations, the variety and frequency of reports of increased incidence of adverse perinatal outcomes following a maternal SARS-CoV-2 infection is concerning. A maternal SARS-CoV-2 infection should be considered a risk factor for pregnancy and pregnant people should be offered enhanced prenatal care following a reported infection.

3.4. Discussion of SARS-CoV-2 infection impact on maternal-fetal outcomes

Pregnancy increases the risk of more severe COVID-19 outcomes and people with COVID-19 during pregnancy have worse maternal outcomes than those that do not[1–16]. Unfortunately, throughout the pandemic COVID-19 has disproportionately impacted pregnant people who are more vulnerable [10,11,15,16,18,30,36–39]. COVID-19 also increases the risk for several perinatal outcomes, which can have a lifelong impact on a child's health [7,10–14,16,18–20,25,26,30,31,33,36–38,53–59]. Furthermore, the COVID-19 pandemic has been a rapidly evolving situation with differences in transmissibility and severity observed between variants complicating our understanding of the impact of COVID-19 on maternal-fetal outcomes [7,19–24,49]. All this combines underlines the necessity to ensure the risk of COVID-19 is reduced in this population. Pregnant people should be encouraged to become vaccinated and stay current with their COVID-19 vaccination schedule as part of routine prenatal care to reduce their risk of infection. Pregnant people should also report SARS-CoV-2 infections to their doctor so that they can receive enhanced prenatal care. More effort should be made to identify subpopulations of people that are most at risk for adverse maternal-fetal outcomes and identify interventions that promote healthy pregnancy outcomes following a maternal SARS-CoV-2 infection.

4. COVID-19 vaccination and pregnancy

Pregnant people were initially excluded from all clinical trials for COVID-19 vaccinations, and there are still no clinical trials that have reported results. Due to a lack of safety and efficacy data on COVID-19 vaccines during pregnancy there was initially mixed messaging on the vaccination of pregnant people by top health organizations [60]. This has contributed to global vaccine hesitancy in pregnant people with common reasons being the lack of safety and efficacy data and about the vaccine potentially harmful side effects to their developing baby [61–64]. Following the release of COVID-19 vaccinations, studies have reported decreased rates of maternal SARS-CoV-2 infection and reduced COVID-19 severity compared to unvaccinated pregnant people [20]. In addition, there are no reports of adverse effects in birth outcomes following COVID-19 vaccination [19,20,65–67]. Similarly, initial studies on booster shots have reported that pregnant people with 3-doses compared to 2-doses have better maternal-fetal outcomes.[20]. The results of these retrospective studies on the positive impact of COVID-19 vaccination on maternal-fetal outcomes should help alleviate vaccine hesitancy in the pregnant population. They also should inform clinical, policy, and research decisions regarding COVID-19 vaccination in pregnant people. Altogether, they promote that pregnant people should be vaccinated and remain current with their COVID-19 vaccination schedule.

4.1. History of guidelines for COVID-19 vaccination during pregnancy

The first COVID-19 vaccine became available under emergency-use authorization in the United States on December 11, 2020. However, there was no guidance on the vaccine use in pregnant people upon release. In January 2021 there was mixed messaging by both the CDC and the World Health Organization (WHO) about COVID-19 vaccination during pregnancy due to the lack of safety and efficacy data of COVID-19 vaccination in pregnant people [60]. On January 7, 2021, the CDC stated that vaccination during pregnancy was a personal choice [60]. The CDC first recommended that pregnant people receive the COVID-19 vaccine on April 23, 2021 - more than 5 months after the first COVID-19 vaccine became available [68]. As more data accrued about the safety and efficacy of COVID-19 vaccinations in pregnant people, this recommendation was strengthened on August 11, 2021 to encourage all pregnant people to get vaccinated against COVID-19 [69]. Meanwhile, the WHO initially recommended against vaccinating pregnant people unless they were at high risk for exposure or severe disease in January 2021 [60]. By February of 2022 the WHO noted that pregnant people should have access to all WHO-EUL approved COVID-19 vaccines and that "the benefits of vaccination during pregnancy outweigh potential risks" [70]. Professional societies American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine also recommend that pregnant people be vaccinated against COVID-19 on July 30, 2021 [71].

4.2. Vaccine hesitancy during pregnancy and discrepancies in vaccine uptake

Vaccine hesitancy in the pregnant population was high in the months leading up to and following the release of COVID-19 vaccines with 22.6–86.2 % of expectant mothers expressing hesitancy or refusal towards COVID-19 vaccination (Table 3) [61–64,72–86]. Vaccine hesitancy has also been reported to be higher in pregnant people than non-pregnant women of reproductive age [82]. This hesitancy is understandable given the lack of safety and efficacy data and mixed messaging from health agencies during the first few months of COVID-19 vaccines becoming available. In addition, vaccine hesitancy is not a new phenomenon with childhood immunization rates declining over recent years due to a broad range of factors [87,88]. Acceptance of the influenza vaccine and other routine vaccines is positively associated with COVID-19 vaccine acceptance, which suggests that there is a broader and deeper issue of vaccine hesitancy in pregnant people.[41,61,62,64,72,77,79,89]. Consistently the most common concern amongst pregnant people that were vaccine hesitant was the vaccine potentially causing harmful side effects to their developing baby and another common concern was the lack of safety and efficacy data of the COVID-19 vaccine during pregnancy [61–64,73,74,77,78,80,84–86]. Despite this, pregnant people report lower rates of common side effects after both first and second doses of COVID-19 vaccines compared to matched non-pregnant female controls [90]. This discrepancy in expectations versus reality may partially be explained due to prevalent lack of knowledge about COVID-19 vaccines amongst vaccine hesitant pregnant people [72,74,76,79,85,86]. Fortunately, being informed about COVID-19 complications in pregnancy was positively associated with COVID-19 vaccination [80]. Together this suggests an opportunity to reduce vaccine hesitancy in the pregnant population through COVID-19 vaccine educational campaigns.

Among pregnant people, vaccine hesitancy was higher in certain groups. Younger age, living in more rural areas, lower educational attainment, and unemployment, were significantly associated with vaccine hesitancy [62,63,74,76–80]. An exception in these reports was a study out of mainland China which reported higher vaccine acceptance in people with lower educational attainment and younger age [73]. Another concern that is unique to pregnant people and women of reproductive age is that the COVID-19 vaccine may lead to infertility [43]. However, studies have reported no impact of COVID-19 vaccination on female fertility.[91–94] Vaccine hesitancy was significantly higher among people that identified as Black, Hispanic, or mixed race [41,62,77]. It is important to recognize that hesitancy in communities that are Black, Indigenous, or People of Color (BIPOC) have roots in structural, historical, and contemporary contexts [43,95]. A multilevel approach is needed to address systemic barriers to vaccine access, and to

develop tailored outreach to promote community engagement and reduce vaccine hesitancy [88,95,96]. Programs that are designed to encourage vaccination should take into account the limited number of approaches that have previously been shown effective at reducing vaccine hesitancy in childhood immunizations including multicomponent and dialogue-based interventions [96].

Vaccination rates in pregnant people lagged behind non-pregnant women of reproductive age with 55 % fewer pregnant people vaccinated compared to non-pregnant women in the US as of May 8, 2021 [40]. Low vaccination rates in pregnant people were also observed in six European countries with 20–80 % vaccinated as of December 2021 [24]. Concerningly, there is evidence that vaccine hesitation persists overtime with few individuals that initially report vaccination hesitation at baseline becoming vaccinated at follow-up [41]. Furthermore, within the pregnant population there have been lower rates of vaccination in younger people, people in rural communities, people of lower socioeconomic status, and people identifying as Black, Hispanic, Indiginous, or multiracial [19,20,40–45]. This illustrates the need for outreach to encourage, promote, and provide opportunities for vaccination and boosters in populations with lower rates. The desire and ability to be vaccinated against COVID-19 is a deeply personal and complex issue. Additional research should be done into other underlying factors such as social determinants of health, rural versus urban, and other potential factors that may contribute to differences in vaccination uptake as well as effective ways to engage communities with the lowest vaccination rates. (Table 5).

4.3. COVID-19 vaccination effect on maternal-fetal outcomes

Vaccinated pregnant people have a significantly lower rate of maternal SARS-CoV-2 infections [20,97–99]. Vaccine efficacy waned overtime in pregnant people [20] similarly to what has been reported in non-pregnant adults [100,101]. A disproportionate number of COVID-19 breakthrough infections in vaccinated pregnant people were during Omicron dominance suggesting that the vaccine was less efficacious at preventing Omicron infection [20] similarly to what has been reported in non-pregnant adults [100,102,103].

There have been varying reports on the impact of COVID-19 vaccination on infection severity in pregnant people, however, most studies indicate COVID-19 vaccination decreases the risk for developing severe COVID-19 in pregnant people. Maternal mortality from COVID-19 occurs more frequently in unvaccinated pregnant people, although this event remains rare [20,44,104,105]. In addition, multiple studies report all or most severe COVID-19 outcomes were in unvaccinated people [19,24,44,104–106]. ICU admissions were reported in unvaccinated people in 80–100 % of cases [19,24,44,105]. There was an overall 16–37 % reduction in COVID-19-related ICU admission and 18–74 % reduction in COVID-19-related intubation in vaccinated people.[44,105] In contrast, Goldshtein et al. observed no difference in the rate of symptomatic versus asymptomatic infections based on vaccination status in pregnant people [65]. Finally, Piekos et al. reported during Omicron dominance in the western U.S. there was no difference in overall COVID-19-associated hospitalization rate based on vaccination status [20]. However, compared to unvaccinated pregnant people, vaccinated pregnant people had significantly lower rates of supplemental oxygen (38 % reduction) or vasopressor (53 % reduction) use during a SARS-CoV-2 infection suggesting that they were less likely to suffer more severe outcomes during a maternal SAR-CoV-2 infection [20]. Altogether, the results are mixed for whether vaccination ameliorates symptoms in mild-moderate COVID-19, though vaccines do appear to limit the development of severe COVID-19. Interpretation of existing studies is often limited by failure to take into account the COVID-19 variant of infection and small sample size for rare outcomes like severe COVID-19 and maternal death. Future large population studies are needed to more completely assess the role of vaccination status on the severity of COVID-19 during pregnancy, especially those that take into

Table 5
COVID-19 vaccine hesitancy rates around the world.

	Study	Study Period	Study Setting	Study Size (n)	Vaccine Hesitancy Rate (n (%))
1	Ayhan et al. 2021	1/1/21–2/1/21	Ankara, Turkey	300	189 (63.0 %)
2	Aynalem et al. 2022	9/1/21–10/30/21	Debre Markos, Ethiopia	350	285 (81.4 %)
3	Battarbee et al. 2021	8/9/20 – 12/10/20	Salt Lake City, Utah, USA; Birmingham, Alabama, USA; and New York, New York, USA	915	541 (59.1 %)
4	Ceulemans et al. 2021	6/16/20–7/14/20	Belgium, Ireland, Norway, Switzerland, The Netherlands, and United Kingdom	6,420	2,477 (38.6 %)
5	Citu et al. 2022	10/1/21–12/1/21	Timisoara, Romania	184	96 (52.2 %)
6	DesJardin et al. 2022	9/1/21–10/31/21	central New York, USA	157	97 (61.7 %)
7	Firouzbakht et al. 2022	10/23–21–1/4/22	Mazandran Province, Iran	352	150 (42.6 %)
8	Gupta et al. 2022	7/31/21–8/24/21	Imphal, Manipur, India	163	101 (62.0 %)
9	Hosokawa et al. 2022	7/28/21–8/30/21	Japan	1,621	825 (50.9 %)
10	Kiefler et al. 2021	3/22/21–4/2/21	Columbus, Ohio, USA	456	212 (46.5 %)
11	Kumari et al. 2022	11/1/21–12/31/21	New Delhi, India	313	89 (28.4 %)
12	Nowacka et al. 2022	12/1/21–4/1/22	Warsaw, Poland	1,033	324 (31.4 %)
13	Riad et al. 2021	8/1/21–9/30/21	Líškovec, Czechia	278	65 (23.4 %)
14	Saitoh, Takaku, & Saitoh 2022	9/1/20–12/31/20	Niigata City, Tokyo	113	46 (40.7 %)
15	Schaal et al. 2022	3/30/21–4/19/21	Germany	1,018	878 (86.2 %)
16	Simmons et al. 2022	12/24/20–1/27/21	California, USA	387	220 (56.8 %)
17	Skjefte et al. 2021	10/28/20–11/18/20	Argentina, Australia, Brazil, Chile, Columbia, India, Italy, Mexico, New Zealand, Peru, Philipines, Russia, Spain, South Africa, United Kingdom, United States	5,294	2,547 (48.1 %)
18	Tao et al. 2021	11/13/20–11/27/20	Mainland China	1,392	315 (22.6 %)
19	Ward et al. 2022	9/1/21–10/31/21	Western Australia	218	122 (56.0 %)

account the probable COVID-19 variant.

There have now been several large population studies that examine the impact of COVID-19 vaccination on birth outcomes [19,20,45,65–67,107–111]. Lower rates of very preterm birth (<32 weeks gestation) was observed in vaccinated pregnant people in Ontario, Canada (34 % reduction) and Sweden (22 % reduction) [67], but no difference was observed in Norway [67]. Several studies reported no association of vaccination status with preterm birth, stillbirth, small for gestational age, very low birth weight, infant mortality, or neonatal hospitalizations [19,20,45,65–67,106–108,110,111]. Two studies reported 40–43 % reductions in the rate of stillbirth in vaccinated people and the effect remained even after adjusting for common cofactors [20,110]. Another reported a slight decrease in risk for NICU admission in babies born to people receiving at least one-dose compared to those born to unvaccinated people [109]. The time period of this study included multiple waves of Omicron and subsequent variants over several months, unlike the previous studies, which might account for the difference in observation of stillbirth rate among vaccinated pregnant people. Altogether, the vaccines consistently are shown to have neutral or positive effects on birth outcomes. This should provide reassurance for concerns about COVID-19 vaccination impact on the developing baby, one of the most commonly stated reasons for COVID-19 vaccine hesitancy [61–64,73,74,77,78,80,84–86].

In addition, COVID-19 vaccination during pregnancy can protect the baby from COVID-19 after delivery. COVID-19 vaccination during pregnancy allows antibodies to pass through the umbilical cord to the fetus *in utero*, which can protect the fetus against maternal SARS-CoV-2 infection [112–114]. Maternal and umbilical cord IgG antibodies were lowest following first trimester vaccination and highest following third trimester vaccination in pregnant people with no history of COVID-19 [114]. Maternal and umbilical cord IgG antibody levels were higher in pregnant people with a prior SARS-CoV-2 infection than those with no history of COVID-19 regardless of the timing of vaccine administration [114]. Babies born to mothers who received a two dose mRNA vaccination series during pregnancy had a 30 % reduction of COVID-19-associated ICU admission during the first six months of life [115].

In summary, the data show that COVID-19 vaccination reduces the risk of maternal infection, and has neutral to positive effects on birth outcomes. It also conveys immunogenicity to the fetus with the highest levels of umbilical IgG antibodies detected following third trimester vaccination. Following birth, this protects the baby from COVID-19 during their first six months of life. Therefore, COVID-19 vaccination during pregnancy benefits both maternal and fetal health.

4.4. Initial evaluation of booster shots in pregnant people

While there is limited information on the impact of booster shots during pregnancy, they are recommended at least six months after the initial vaccination series. In the general population, three doses of the COVID-19 vaccine has higher efficacy compared to two doses, although vaccine efficacy wanes over time [100–102]. One study including 7,616 people boosted at time of delivery reports a 50 % reduction in maternal SARS-CoV-2 infection and 18 % reduction in COVID-19-related hospitalization rate in people that received three doses of mRNA vaccine compared to those that received two.[20] They also report significantly lower rates of preterm birth (15 % reduction), stillbirth (50 % reduction), SGA (9 % reduction), and very low birth weight (<1500 g; 33 % reduction) in boosted compared to vaccinated, but not boosted people [20]. A limited study of 294 boosted people reported similar rates of preterm birth and SGA between people receiving 3-doses versus 2-doses, but a higher rate of postpartum hemorrhaging (OR=3.34 95 % CI=[2.07,5.39]) [116]. Differences in the results between these two studies could be attributed to the difference in sample size as well as differences in the time from last vaccine dose in the 2-dose groups. This highlights the need for additional large multicenter retrospective cohort studies to establish the impact of COVID-19 booster shots on maternal-fetal health.

In addition, administration of booster shots during pregnancy resulted in transfer of antibodies to the developing fetus [114]. Excitingly, the maternal and umbilical IgG levels in 20 boosted individuals and reported the highest maternal and umbilical IgG levels in boosted individuals compared to fully vaccinated individuals regardless of the trimester of vaccination administration [114]. This suggests that booster shots convey additional immune protection to the baby when they are administered during pregnancy. These studies offer some support that booster shots promote immunity and positive maternal-fetal outcomes. We expect future studies to further investigate the role of a third and if approved later additional doses of COVID-19 vaccination on maternal-fetal health.

5. Conclusion

COVID-19 during pregnancy adversely affects maternal-fetal health. Pregnant people are at increased risk for more severe COVID-19 compared to non-pregnant adults including increased risk for severe disease, hospitalization, ICU admission, and death. Maternal SARS-CoV-2 infections also increase risk for negative birth outcomes including preterm birth and stillbirth. COVID-19 vaccination offers a way to protect both maternal and fetal health by reducing the risk of maternal SARS-CoV-2 infection. Unfortunately, the lack of safety and efficacy data upon the initial release of the COVID-19 vaccines led to mixed messaging on COVID-19 vaccination in pregnant people contributing to vaccine hesitancy in this population. However, several recent studies show that vaccines are safe and effective in pregnant people including decreased risk for infection and severe disease as well as transferring of antibodies to the baby. Studies have also reported neutral rates of preterm birth, stillbirth, SGA, and low birth weight in vaccinated people with one study reporting a 40 % reduction in stillbirth in vaccinated people. Although there is limited data of booster shots during pregnancy, initial studies report improved maternal-fetal outcomes in boosted compared to vaccinated, but not boosted people. Altogether, this indicates that an effective way to promote maternal-fetal health is to encourage pregnant people to become vaccinated and stay up to date with their COVID-19 vaccine.

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CRediT authorship contribution statement

SNP performed literature search and wrote the first draft of the manuscript. SNP, NDP, and JJH contributed to the manuscript conception, revision, read, and approved the submitted version. SNP, NDP, and LH secured funding to support this work.

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