RESEARCH

The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis

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Cite as: *CMAJ* 2021 April 19;193:E540-8. doi: 10.1503/cmaj.202604; early-released March 19, 2021

ABSTRACT

Background: The impact of coronavirus disease 2019 (COVID-19) on maternal and newborn health is unclear. We aimed to evaluate the association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy and adverse pregnancy outcomes.

METHODS: We conducted a systematic review and meta-analysis of observational studies with comparison data on SARS-CoV-2 infection and severity of COVID-19 during pregnancy. We searched for eligible studies in MEDLINE, Embase, ClinicalTrials.gov, medRxiv and Cochrane databases up to Jan. 29, 2021, using Medical Subject Headings terms and keywords for "severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2 OR coronavirus disease 2019 OR COVID-19" AND "pregnancy." We evaluated the methodologic quality of all included studies using the Newcastle-Ottawa Scale. Our primary outcomes were preeclampsia and preterm birth. Secondary outcomes included stillbirth, gestational diabetes and other pregnancy outcomes. We calculated summary odds ratios (ORs) or weighted mean differences with 95% confidence intervals (CI) using random-effects meta-analysis.

RESULTS: We included 42 studies involving 438 548 people who were pregnant. Compared with no SARS-CoV-2 infection in pregnancy, COVID-19 was associated with preeclampsia (OR 1.33, 95% CI 1.03 to 1.73), preterm birth (OR 1.82, 95% CI 1.38 to 2.39) and stillbirth (OR 2.11, 95% CI 1.14 to 3.90). Compared with mild COVID-19, severe COVID-19 was strongly associated with preeclampsia (OR 4.16, 95% CI 1.55 to 11.15), preterm birth (OR 4.29, 95% CI 2.41 to 7.63), gestational diabetes (OR 1.99, 95% CI 1.09 to 3.64) and low birth weight (OR 1.89, 95% CI 1.14 to 3.12).

INTERPRETATION: COVID-19 may be associated with increased risks of preeclampsia, preterm birth and other adverse pregnancy outcomes.

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was declared a global pandemic in March 2020.[1] Pregnant people and infants may be particularly susceptible to COVID-19 because the physiologic changes of pregnancy involve cardiorespiratory and immune systems, which may result in an altered response to SARS-CoV-2 infection in pregnancy.[2] Fetuses may be exposed to SARS-CoV-2 during critical periods of fetal development.[3] The nature of the association between COVID-19 and pregnancy outcomes remains unclear, and meta-analyses involving patients with COVID-19 who are pregnant are limited. Previous reviews have focused mostly on prevalence estimates from case reports or case series that are difficult to interpret and potentially biased.[4,5] A 2020 systematic review suggested that people who are pregnant did not have an increased risk of SARS-CoV-2 infection or symptomatic COVID-19, but they were at risk of severe COVID-19 compared with those who were not pregnant.[5] However, this review included suspected COVID-19 cases in addition to confirmed cases.[5] Although some recent observational studies have suggested that people with confirmed asymptomatic and symptomatic COVID-19,[6–15] as well as mild and severe infections,[6,8,9,15–22] may be at risk of adverse pregnancy outcomes, we are unaware of any systematic reviews that have comprehensively evaluated these data.

We performed a systematic review and meta-analysis of maternal, fetal and neonatal outcomes among pregnant patients with COVID-19. We aimed to determine the association between SARS-CoV-2 infection and adverse pregnancy outcomes, including preeclampsia, preterm birth and stillbirth.

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Methods

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data sources, search strategy and study selection

We performed a systematic search of MEDLINE, Embase, ClinicalTrials.gov, medRxiv and Cochrane databases up to Jan. 29, 2021, to identify observational studies with comparative data for people with COVID-19 who were pregnant (Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.202604/tab-related-content). Our search strategy followed the Peer Review of Electronic Search Strategies (PRESS) guidelines. We searched the databases using a combination of Medical Subject Headings (MeSH) terms and keywords for "severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2 OR 2019 novel coronavirus OR COVID-19" AND "pregnancy," with language restricted to English abstracts. We also manually searched references cited in these articles to identify any additional studies.

Two investigators independently screened the titles and abstracts identified by the electronic searches, compared selected studies and resolved discrepancies by discussion.

We scrutinized and selected full-length articles of studies evaluating COVID-19 in pregnancy and maternal and infant outcomes that met the following inclusion criteria: observational study; population included pregnant people; SARS-CoV-2 infection was confirmed by a polymerase chain reaction (PCR) test or with codes for confirmed COVID-19 from the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10); comparisons included patients with COVID-19 versus those without COVID-19, patients with symptomatic versus those with asymptomatic COVID-19, or severe versus mild COVID-19; outcomes included maternal, fetal or neonatal morbidity and mortality; comparative data needed to calculate effect sizes were available; and methodologic quality assessment criteria in the Newcastle–Ottawa Scale suggested low or moderate risk of bias.[23]

We excluded studies that met at least 1 of the following exclusion criteria: reviews, case reports or case series; studies with no comparison data; and studies that included cases of infective pneumonia caused by other viral agents. If more than 1 study was published that involved the same cohort with identical outcomes, we included the report containing the most comprehensive information to avoid including the same data twice.

Case definition

We defined cases of COVID-19 as confirmed SARS-CoV-2 infection in a person who was pregnant. Controls without COVID-19 included pregnant people with negative PCR tests, those who were pregnant before the pandemic or those who were pregnant and asymptomatic early in the pandemic. We defined asymptomatic COVID-19 as a positive test result for SARS-CoV-2 in a patient who never developed symptoms of COVID-19 and symptomatic COVID-19 as a positive test result for SARS-CoV-2 with the development of fever, cough, shortness of breath, fatigue, or loss of taste or smell. We defined severe COVID-19 as the presence of dyspnea, respiratory rate at 30 breaths per minute or more and oxygen saturation at 93% or less on room air, or findings consistent with pneumonia.[24] We defined mild COVID-19 as a positive test result for SARS-CoV-2 without development of severe symptoms. We classified cases of COVID-19 as symptomatic or asymptomatic and severe or mild. For symptomatic COVID-19, we included patients with any symptom regardless of severity. For severe COVID-19, we included patients with severe and critical symptoms, whereas mild COVID-19 included asymptomatic or mild cases.[6,7,19]

Outcomes

We selected outcomes based on clinical importance and availability in published studies. Our primary outcomes included preeclampsia and preterm birth. Our secondary outcomes were gestational diabetes, chorioamnionitis or intra-amniotic infection, cesarean delivery, abnormal liver function, lymphopenia, mechanical ventilation, admission to the intensive care unit (ICU), stillbirth (fetal loss at the 20th week of pregnancy or later), fetal distress, birth weight, low birth weight, gestational age at birth, admission to the neonatal ICU (NICU) and neonatal death.

Assessment of study quality

Two reviewers independently assessed the methodologic quality of each study using the Newcastle–Ottawa Scale.[23] Cohort studies were evaluated for the following 3 domains: quality of selection of cohorts (4 stars), comparability of cohorts (2 stars) and assessment of outcome (3 stars). Case–control studies were assessed for quality of selection of cases and controls (4 stars), comparability of cases and controls (2 stars) and ascertainment of exposure (3 stars). We considered a total of 7 out of 9 stars to be a low risk of bias, 4–6 stars to be a moderate risk and less than 4 stars to be a high risk of bias (Appendix 2, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.202604/tab-related-content). In case of a disagreement, reviewers reached consensus by discussion with a third reviewer.

Data extraction and analysis

Two authors extracted data independently and in duplicate, with any discrepancy resolved by discussion. Data were extracted and statistical analysis carried out using Review Manager 5.4. We used unadjusted estimates for meta-analysis because most of the studies reported only data for raw outcomes. We used the Mantel–Haenszel method to combine data on dichotomous outcomes, and measures of effect are presented as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous data, we calculated the sample size weighted mean difference (MD) when outcomes were measured the same way between studies. We assessed the associations between COVID-19 morbidity and pregnancy outcomes (patients with COVID-19 versus pregnant people with no SARS-CoV-2 infection). We also evaluated outcomes of COVID-19 severity in pregnant patients with confirmed infection (symptomatic versus asymptomatic and severe versus mild COVID-19).

We used forest plots to show individual point estimates (95% CIs) for each study, and a diamond to represent the pooled point estimate (95% CI) for each outcome of interest. We evaluated heterogeneity with the I^2 statistic. If the I^2 value was 40% or greater, we considered heterogeneity to be present.[25] We pooled results using random-effects models. We performed a sensitivity analysis that

excluded preprints and studies with moderate risk of bias and used fixed-effect models for outcomes from studies with small numbers of patients. We used funnel plots to assess publication bias.

Ethics approval

Ethics approval was not sought for this systematic review because the data were publicly available.

Results

We found 7212 potentially relevant citations using our search strategy. The PRISMA flow diagram (Figure 1) summarizes the process of literature search and selection of studies. After screening titles and abstracts, we read 357 full-text articles. Forty-two observational studies[7–15,17,19,21,22,26–54] involving 438 548 pregnant people met the inclusion criteria and were included in the systematic review and meta-analysis. Our assessment of the methodologic quality of each eligible study is summarized in Appendix 2. Ninety-five percent (40 out of 42) of the observational studies had an overall low risk of bias according to the Newcastle–Ottawa Scale, and 5% (2 out of 42) of the studies had moderate risk.

Characteristics of the included studies are summarized in Appendix 3, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.202604/tab-related-content. Of the 42 studies, 16 were prospective cohorts,[7,9,11,18,19,21,28,30,33,34,36,37,46,49–51] 21 were retrospective cohorts[8,10,12–14,17,27,29,32,35,38–45,48,53,54] and 5 were case–control

Figure 1: Flow chart for the selection of studies.

studies.[22,31,47,50,52] One prospective study resulted in 2 publications, 1 preprint study for positive versus negative SARS-CoV-2 infection[34] and another for severe versus mild COVID-19.[18] Cases of COVID-19 were confirmed by PCR testing. There were 28 studies of confirmed versus no SARS-CoV-2 infection in pregnancy.[11–13,15,22,27–32,34,35,37,39–45,47–51,53,54] Twelve studies compared symptomatic versus asymptomatic COVID-19.[7–15,46,48,52] There were 13 studies of severe versus mild COVID-19 in pregnancy.[8,9,15,17–19,21,22,26,33,36,38,48]

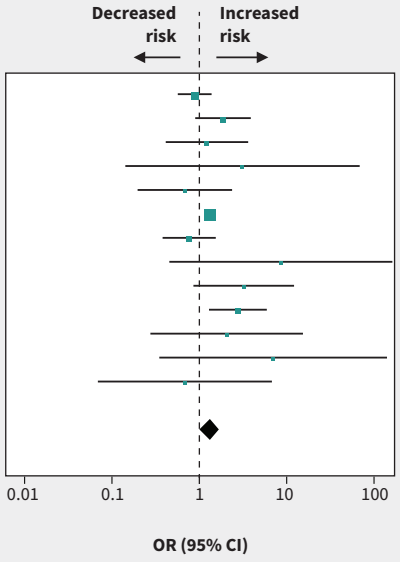
Compared with no infection, we found that SARS-CoV-2 infection in pregnancy was associated with preeclampsia (OR 1.33, 95% CI 1.03 to 1.73; I^2 = 31%; based on 13 studies) (Figure 2A), preterm birth (OR 1.82, 95% CI 1.38 to 2.39; I^2 = 64%; 18 studies) (Figure 3A), stillbirth (OR 2.11, 95% CI 1.14 to 3.90; I^2 = 24%; 6 studies) (Figure 4), ICU admission (OR 4.78, 95% CI 2.03 to 11.25; I^2 = 76%; 5 studies), lower birth weight (grams; mean difference −68.96, 95% CI −130.22 to −7.69; I^2 = 29%; 13 studies) and NICU admission (OR 3.69, 95% CI 1.39 to 9.82; I^2 = 94%; 10 studies) (Appendix 4, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.202604/tab-related-content). COVID-19 was not associated with gestational diabetes, cesarean delivery, postpartum hemorrhage or neonatal death compared with no COVID-19 (Table 1).

Compared with asymptomatic COVID-19, symptomatic COVID-19 in pregnancy was associated with increased risk of preterm birth (OR 2.29, 95% CI 1.49 to 3.53; I^2 = 57%; based on 9 studies) (Figure 3B) and cesarean delivery (OR 1.57, 95% CI 1.32 to 1.85; I^2 = 1%; 9 studies) (Appendix 4). Symptomatic COVID-19 was not associated with gestational diabetes (Table 1).

Compared with mild COVID-19, severe COVID-19 was strongly associated with preeclampsia (OR 4.16, 95% CI 1.55 to 11.15; I^2 = 0%; based on 5 studies) (Figure 2C), preterm birth (OR 4.29, 95% CI 2.41 to 7.63; I^2 = 61%; 10 studies) (Figure 3C), gestational diabetes (OR 1.99, 95% CI 1.09 to 3.64; I^2 = 14%; 5 studies), ICU admission (OR 15.46, 95% CI 5.79 to 41.23; I^2 = 0%; 5 studies), mechanical ventilation (OR 19.31, 95% CI 9.38 to 39.72; I^2 = 0%; 5 studies), cesarean delivery (OR 2.58, 95% CI 1.64 to 4.06; I^2 = 43%; 8 studies), low birth weight (OR 1.89, 95% CI 1.14 to 3.12; I^2 = 0%; 2 studies) and NICU admission (OR 3.95, 95% CI 1.43 to 10.95; I^2 = 79%; 5 studies) (Table 1, Appendix 4).

A

Study or subgroup	COVID-19 Events	COVID-19 Total	No COVID-19 Events	No COVID-19 Total	OR (95% CI)
Adhikari et al.[48]	26	245	359	3035	0.88 (0.58 to 1.35)
Ahlberg et al.[43]	12	155	26	604	1.87 (0.92 to 3.79)
Brandt et al.[22]	6	61	10	122	1.22 (0.42 to 3.53)
Erol et al.[50]	2	60	0	36	3.12 (0.15 to 66.83)
Gulersen et al.[29]	5	50	7	50	0.68 (0.20 to 2.32)
Jering et al.[53]	564	6380	27 078	400 066	1.34 (1.22 to 1.46)
Martínez-Perez et al.[18]	11	246	44	763	0.76 (0.39 to 1.51)
Patberg et al.[41]	5	77	0	56	8.57 (0.46 to 158.29)
Pirjani et al.[37]	6	66	4	133	3.23 (0.88 to 11.85)
Wang et al.[39]	10	53	59	760	2.76 (1.32 to 5.78)
Yang et al.[42]	1	65	83	11 013	2.06 (0.28 to 15.01)
Yazihan et al.[47]	3	95	0	92	7.00 (0.36 to 137.43)
Zhang et al.[40]	1	16	4	45	0.68 (0.07 to 6.61)
Total (95% CI)		7569		416 775	1.33 (1.03 to 1.73)
Total events	652		27 674		
Heterogeneity: I^2 = 31%					



B

Study or subgroup	Severe COVID-19 Events	Severe COVID-19 Total	Mild COVID-19 Events	Mild COVID-19 Total	OR (95% CI)
Adhikari et al.[48]	2	12	24	233	1.74 (0.36 to 8.42)
Barbero et al.[26]	3	42	0	49	8.77 (0.44 to 174.89)
Brandt et al.[22]	2	7	4	54	5.00 (0.73 to 34.46)
Martínez-Perez et al.[18]	1	4	3	78	8.33 (0.66 to 105.71)
Mendoza et al.[19]	1	8	0	34	13.80 (0.51 to 372.88)
Total (95% CI)		73		448	4.16 (1.55 to 11.15)
Total events	9		31		
Heterogeneity: I^2 = 0%					

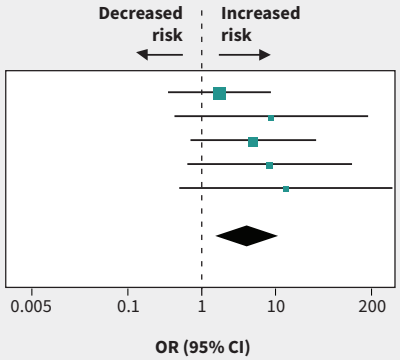
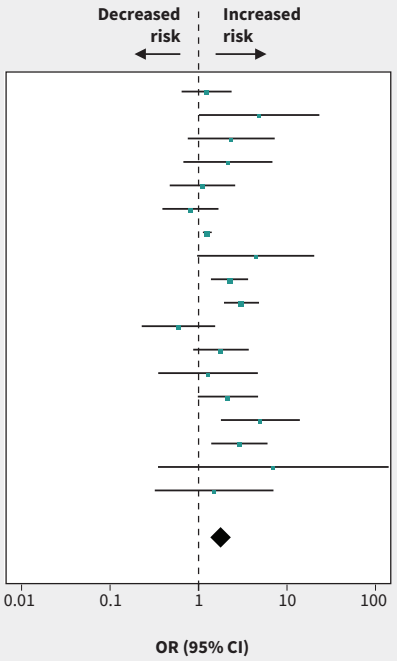


Figure 2: Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the association between coronavirus disease 2019 (COVID-19) and preeclampsia. (A) Association between COVID-19 and preeclampsia (patients with COVID-19 versus patients without COVID-19). (B) Association between severe COVID-19 and preeclampsia (patients with severe versus mild COVID-19).

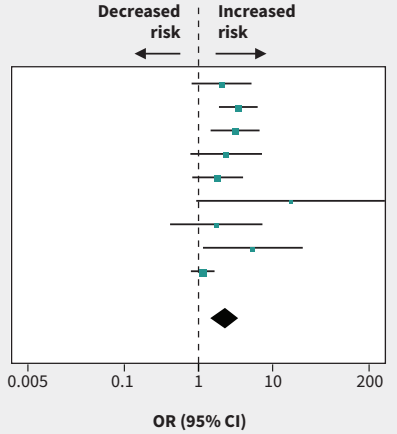
A

Study or subgroup	COVID-19 Events	COVID-19 Total	No COVID-19 Events	No COVID-19 Total	OR (95% CI)
Ahlberg et al.[43]	14	155	45	604	1.23 (0.66 to 2.31)
Cunarro-Lopez et al.[44]	13	68	2	43	4.85 (1.04 to 22.66)
Diaz-Corvillon et al.[15]	4	37	27	549	2.34 (0.77 to 7.09)
Edlow et al.[49]	10	64	5	63	2.15 (0.69 to 6.69)
Flaherman et al.[27]	21	179	9	84	1.11 (0.48 to 2.53)
Hcini et al.[51]	11	137	36	370	0.81 (0.40 to 1.64)
Jering et al.[53]	459	6380	23 234	400 066	1.26 (1.14 to 1.38)
Li et al.[31]	3	16	6	121	4.42 (0.99 to 19.82)
Martínez-Perez et al.[18]	34	246	51	763	2.24 (1.41 to 3.55)
Nayak et al.[35]	38	141	90	836	3.06 (1.99 to 4.71)
Pineles et al.[54]	5	77	90	858	0.59 (0.23 to 1.51)
Prabhu et al.[11]	11	70	57	605	1.79 (0.89 to 3.61)
Smithgall et al.[13]	10	51	4	25	1.28 (0.36 to 4.57)
Wang et al.[39]	9	53	66	760	2.15 (1.01 to 4.60)
Woodworth et al.[46]	8	16	99	594	5.00 (1.83 to 13.64)
Yang et al.[42]	9	65	579	11 013	2.90 (1.43 to 5.88)
Yazihan et al.[47]	3	95	0	92	7.00 (0.36 to 137.43)
Zhang et al.[40]	3	16	6	45	1.50 (0.33 to 6.87)
Total (95% CI)		7866		417 491	1.82 (1.38 to 2.39)
Total events	665		24 406		
Heterogeneity: I^2 = 64%					



B

Study or subgroup	Symptomatic COVID-19 Events	Symptomatic COVID-19 Total	Asymptomatic COVID-19 Events	Asymptomatic COVID-19 Total	OR (95% CI)
Adhikari et al.[48]	20	147	7	98	2.05 (0.83 to 5.04)
Delahoy et al.[7]	31	134	25	311	3.44 (1.94 to 6.11)
Di Mascio et al.[55]	60	189	10	77	3.12 (1.50 to 6.48)
Jenabi et al.[52]	12	45	6	45	2.36 (0.80 to 6.99)
Khoury et al.[9]	25	139	11	102	1.81 (0.85 to 3.88)
London et al.[10]	9	33	0	22	17.45 (0.96 to 317.38)
Smithgall et al.[13]	6	25	4	26	1.74 (0.43 to 7.09)
Verma et al.[14]	14	89	2	60	5.41 (1.18 to 24.77)
Woodworth et al.[46]	297	2315	43	376	1.14 (0.81 to 1.60)
Total (95% CI)		3116		1117	2.29 (1.49 to 3.53)
Total events	474		108		
Heterogeneity: I^2 = 57%					



C

Study or subgroup	Severe COVID-19 Events	Severe COVID-19 Total	Mild COVID-19 Events	Mild COVID-19 Total	OR (95% CI)
Adhikari et al.[48]	5	12	22	233	6.85 (2.00 to 23.41)
Barbero et al.[26]	5	11	3	12	2.50 (0.43 to 14.61)
Brandt et al.[22]	4	7	3	54	22.67 (3.40 to 151.02)
Di Mascio et al.[55]	60	189	10	77	3.12 (1.50 to 6.48)
Kayem et al.[17]	37	58	13	123	14.91 (6.80 to 32.70)
Khoury et al.[9]	18	73	18	166	2.69 (1.31 to 5.54)
Maraschini et al.[33]	15	47	13	99	3.10 (1.33 to 7.23)
Martínez-Perez et al.[18]	4	4	21	78	24.07 (1.24 to 466.10)
Panagiotakopoulos et al.[36]	5	32	9	61	1.07 (0.33 to 3.51)
Savasi et al.[21]	4	11	8	46	2.71 (0.64 to 11.52)
Total (95% CI)		444		949	4.29 (2.41 to 7.63)
Total events	157		120		
Heterogeneity: I^2 = 61%					

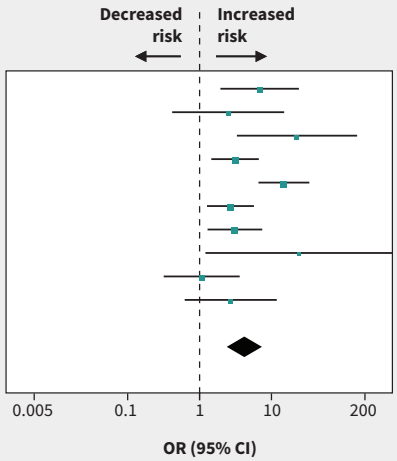


Figure 3: Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the association between coronavirus disease 2019 (COVID-19) and preterm birth. (A) Association between COVID-19 and preterm birth (patients with COVID-19 versus no COVID-19). (B) Association between symptomatic COVID-19 and preterm birth (patients with symptomatic versus asymptomatic COVID-19). (C) Association between severe COVID-19 and preterm birth (patients with severe versus mild COVID-19).

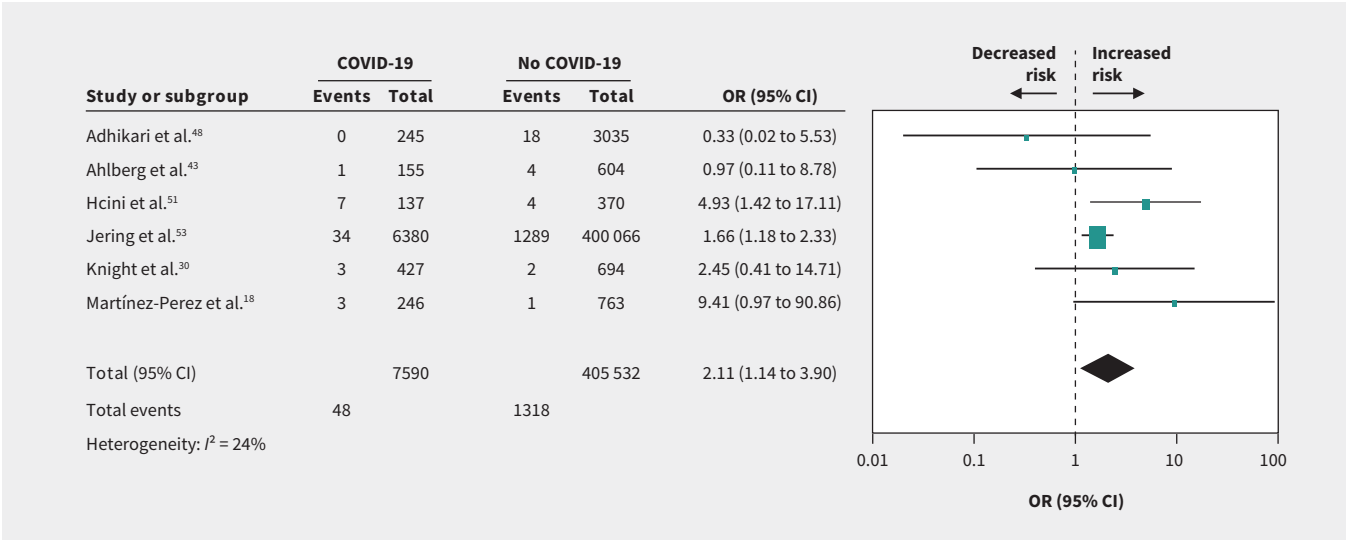


Figure 4: Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the association between coronavirus disease 2019 (COVID-19) and stillbirth.

Sensitivity analyses produced similar results (Appendices 5 and 6, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.202604/tab-related-content). Funnel plots for preeclampsia and preterm birth did not suggest that the conclusions were affected by publication bias (Appendix 7, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.202604/tab-related-content).

Interpretation

We found that COVID-19 in pregnancy is associated with preeclampsia, stillbirth and preterm birth compared with no COVID-19. Symptomatic COVID-19 was associated with an increased risk of cesarean delivery and preterm birth compared with asymptomatic COVID-19. Compared with mild COVID-19, severe COVID-19 was strongly associated with preeclampsia, gestational diabetes, preterm birth and low birth weight. This meta-analysis of observational studies is unique in providing comparative data on COVID-19 morbidity during pregnancy. Our findings suggest that COVID-19 in pregnancy is associated with preeclampsia and preterm birth, and that severe COVID-19 can lead to considerable maternal and neonatal morbidity.

We selected studies with low-to-moderate risk of bias using strict quality assessment criteria.[23] Although the number of publications on COVID-19 in pregnant people continues to increase, previous systematic reviews on COVID-19 in pregnancy have included mainly case reports and case series,[4,5] or reviewed case reports for other types of coronavirus,[55] describing the proportion of patients with clinical manifestations or pregnancy complications. These reviews recognized the lack of good-quality data in the early stage of the pandemic that are needed to draw unbiased conclusions. One of the earliest systematic reviews reported that there was no difference in the clinical characteristics of patients with COVID-19 who were pregnant compared with patients who were not pregnant.[56] A living systematic review that included mainly case reports and case series,[5] many of which used control groups of people who were not pregnant, or did not have a comparison group, reported that pregnant patients were less likely to have COVID-19 symptoms than those with COVID-19 who were not pregnant.[5] Our meta-analysis of recent good-quality cohort studies with comparative data does not align with these previous reviews, and provides clear evidence that symptomatic or severe COVID-19 is associated with a considerable risk of preeclampsia, preterm birth and low birth weight.

The mechanisms underlying the association between COVID-19 and preeclampsia are unclear, but investigators have shown that SARS-CoV-2 may lead to renin–angiotensin system dysfunction and vasoconstriction by binding to angiotensin-converting enzyme 2 receptors.[57] The hallmark of preeclampsia is a systematic endothelial dysfunction, which may share a common pathway with COVID-19 illness as the vascular effects of SARS-CoV-2 infection are increasingly recognized. One study found that people with severe COVID-19 who were pregnant acquired clinical manifestations similar to preeclampsia and were distinguishable by biomarker levels, including serum-soluble *fms*-like tyrosine kinase and placental growth factor.[19] Some studies have shown that SARS-CoV-2 infection may create a proinflammatory state that is followed by systemic endothelial dysfunction and preeclampsia.[58,59] Our finding is consistent with a 2020 study in Sweden that reported that pregnant people with COVID-19 had a higher prevalence of preeclampsia.[43]

Our meta-analysis also suggests that SARS-CoV-2 infection was associated with preterm birth, stillbirth and lower birth weight but not with cesarean delivery, compared with the absence of SARS-CoV-2 infection. We also found that severe COVID-19 was strongly associated with preterm birth and other adverse perinatal outcomes. Some of these excess risks could relate to preeclampsia, although SARS-CoV-2 infection may also cause exaggerated systemic inflammatory responses involved in the pathogenesis of preterm birth or a suboptimal environment for fetal growth and development. Placental fetal vascular malperfusion has been found in placental histopathologic findings in patients with COVID-19 at delivery,[41] which may contribute to fetal growth, stillbirth and preterm birth. A recent national quasi-experimental study in the Netherlands found that COVID-19 mitigation measures were associated with a reduced incidence of preterm birth.[60]

Table 1: Summary of pooled results using random-effects models

Outcome	No. of studies	No. of participants	No. of events	Mean difference (95% CI)	OR (95% CI)	Heterogeneity, %
Patients with COVID-19 versus those without COVID-19						
Preeclampsia	13	424 344	28 326		1.33 (1.03 to 1.73)	31
Gestational diabetes	13	425 890	40 567		1.03 (0.76 to 1.39)	54
Fetal distress	3	874	47		1.50 (0.64 to 3.53)	8
Stillbirth	6	413 122	1366		2.11 (1.14 to 3.90)	24
Chorioamnionitis or intra-amniotic infection	5	4368	433		0.85 (0.57 to 1.26)	0
Admission to the ICU	5	409 737	2012		4.78 (2.03 to 11.25)	76
Cesarean delivery	22	429 366	121 650		1.00 (0.82 to 1.23)	78
Postpartum hemorrhage	5	2981	355		0.89 (0.52 to 1.53)	55
Preterm birth	18	425 357	25 071		1.82 (1.38 to 2.39)	64
Neonatal sex, male	5	11 985	6369		0.97 (0.71 to 1.33)	9
Gestational age at birth, wk	13	4197		−0.24 (−0.49 to 0.00)		61
Birth weight, g	13	2973		−68.96 (−130.22 to −7.69)		29
Low birth weight	2	1054	678		2.32 (0.26 to 21.07)	85
Admission to the NICU	10	5675	785		3.69 (1.39 to 9.82)	94
Neonatal death	5	2838			1.10 (0.41 to 2.95)	0
Patients with symptomatic versus asymptomatic COVID-19						
Gestational hypertension or preeclampsia	8	4122	333		1.20 (0.92 to 1.56)	1
Gestational diabetes	5	3767	256		1.12 (0.82 to 1.55)	0
Mechanical ventilation	3	1023	62		16.29 (3.88 to 68.47)	0
Admission to the ICU	4	1178	97		7.40 (0.48 to 114.24)	76
Cesarean delivery	9	4232	1406		1.57 (1.32 to 1.85)	1
Preterm birth	9	4233	582		2.29 (1.49 to 3.53)	57
Admission to the NICU	4	2365	248		3.47 (0.38 to 31.49)	88
Neonatal death	4	938	11		3.67 (0.88 to 15.29)	0
Patients with severe versus mild COVID-19						
Preeclampsia	5	521	40		4.16 (1.55 to 11.15)	0
Gestational diabetes	5	1140	105		1.99 (1.09 to 3.64)	14
Abnormal liver function	4	350	116		6.47 (2.60 to 16.09)	50
Lymphopenia	4	561	221		3.04 (1.93 to 4.79)	0
Admission to the ICU	5	757	70		15.46 (5.79 to 41.23)	0
Mechanical ventilation	5	962	97		19.31 (9.38 to 39.72)	0
Cesarean delivery	8	1138	452		2.58 (1.64 to 4.06)	43
Preterm birth	10	1393	277		4.29 (2.41 to 7.63)	61
Gestational age at birth, wk	8	709		−3.50 (−5.96 to −1.03)		91
Low birth weight	2	400	74		1.89 (1.14 to 3.12)	0
Admission to the NICU	5	729	160		3.95 (1.43 to 10.95)	79
Neonatal death	3	827	12		33.71 (5.18 to 219.44)	0

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, ICU = intensive care unit, NICU = neonatal intensive care unit, OR = odds ratio.

Lack of knowledge about SARS-CoV-2 infection in pregnancy has raised urgent questions among obstetricians and neonatologists about the risk of maternal, fetal and neonatal morbidity and mortality. There is an urgent need for evidence to guide clinical decisions. Our findings suggest that SARS-CoV-2 infection increases the risk of preeclampsia, stillbirth, preterm birth and NICU admission, and that severe COVID-19 illness in pregnancy is particularly problematic for adverse maternal, fetal and neonatal outcomes. Clinicians should be aware of these adverse outcomes when managing pregnancies in patients with COVID-19 and adopt effective strategies to prevent or reduce risks to patients and fetuses.

Limitations

We did not register our study with the International Prospective Register of Systematic Reviews (PROSPERO), and our literature search was restricted to publications in English. Although we included a comprehensive number of outcomes, we cannot rule out the possibility that some associations were spurious. Some of the included studies (14%) did not require a negative result for a PCR test to be included in the unexposed comparison group.[22,32,37,40,42,47] We estimated unadjusted effect sizes, which may have overestimated risks. The largest study that had data on confounders suggested that associations between COVID-19 and pregnancy outcomes were somewhat attenuated after adjustment, although risks remained elevated for most outcomes.[53] We also could not determine the clinical importance of some of the outcomes. For example, we cannot confirm that all patients admitted to the NICU required critical care. The reason for preterm birth was not clear, including if preterm birth was medically indicated or spontaneous. As the data were observational, we cannot eliminate the possibility of residual confounding.

Conclusion

We found that SARS-CoV-2 infection in pregnancy was associated with risks of preeclampsia, stillbirth, preterm birth and NICU admission. In addition, severe SARS-CoV-2 infection was strongly associated with preeclampsia and other adverse maternal and neonatal outcomes. Future studies are needed to collect more robust data to further validate or substantiate these findings, better understand the pathophysiologic pathways that explain these associations and identify effective strategies to prevent adverse outcomes in pregnant people with COVID-19.

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Competing interests: None declared.

This article has been peer reviewed.

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Contributors: Shu Qin Wei and Nathalie Auger contributed to the conception and design of the study. Shu Qin Wei and Marianne Bilodeau-Bertrand screened the articles and assessed the quality of the studies. Shu Qin Wei and Shiliang Liu performed the data extraction and analysis. Shu Qin Wei drafted the manuscript, and Nathalie Auger, Marianne Bilodeau-Bertrand and Shiliang Liu revised the manuscript critically for important intellectual content. All of the authors contributed to the interpretation of the data, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding: This work was supported by a grant from the Canadian Institutes of Health Research (no. PJT-162300). Nathalie Auger has received a career award from the Fonds de recherche du Québec-Santé (no. 34695).

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Data sharing: All relevant data are provided in the article and the appendices, and are available for use.

Accepted: Mar. 2, 2021

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