JAMA Pediatrics | Original Investigation

Peripartum Outcomes Associated With COVID-19 Vaccination During Pregnancy
A Systematic Review and Meta-analysis

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IMPORTANCE The risk and benefits of COVID-19 vaccination during pregnancy are under investigation. Pooled evidence regarding neonatal and maternal outcomes in association with COVID-19 vaccination during pregnancy is scarce.

OBJECTIVE To evaluate the association between COVID-19 vaccination during pregnancy and peripartum outcomes.

DATA SOURCES PubMed and EMBASE databases were searched on April 5, 2022. Language restrictions were not applied.

STUDY SELECTION Prospective trials and observational studies comparing the individuals who received at least 1 COVID-19 vaccination during pregnancy with those who did not and reporting the neonatal outcomes, including preterm birth, small for gestational age, low Apgar score, neonatal intensive care units (NICU) admission, and intrauterine fetal death (IFD).

DATA EXTRACTION AND SYNTHESIS Two independent investigators extracted relevant data from each study. Odds ratios (ORs) were calculated using a random-effects model. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.

MAIN OUTCOMES AND MEASURES The primary outcomes were the neonatal outcomes, including preterm birth, small for gestational age, low Apgar score, NICU admission, and IFD. The secondary outcomes were maternal outcomes, including maternal SARS-CoV-2 infection, cesarean delivery, postpartum hemorrhage, and chorioamnionitis.

RESULTS Nine observational studies involving 81 349 vaccinated (mean age, 32-35 years) and 255 346 unvaccinated individuals during pregnancy (mean age, 29.5-33 years) were included. COVID-19 vaccination during pregnancy was associated with lower risk of NICU admission (OR, 0.88; 95% CI, 0.80-0.97) and IFD (OR, 0.73; 95% CI, 0.57-0.94), whereas there was no statistically significant association with preterm birth (OR, 0.89; 95% CI, 0.76-1.04), small for gestational age (OR, 0.99; 95% CI, 0.94-1.04), and low Apgar score (OR, 0.94; 95% CI, 0.87-1.02). COVID-19 vaccination during pregnancy was associated with a lower risk of maternal SARS-CoV-2 infection (OR, 0.46; 95% CI, 0.22-0.93), whereas it was not associated with increased risk of cesarean delivery (OR, 1.05; 95% CI, 0.93-1.20), postpartum hemorrhage (OR, 0.95; 95% CI, 0.83-1.07), and chorioamnionitis (OR, 0.95; 95% CI, 0.83-1.07).

CONCLUSIONS AND RELEVANCE COVID-19 vaccination during pregnancy was not associated with an increase in the risk of peripartum outcomes, was associated with a decreased risk of NICU admission, IFD, and maternal SARS-CoV-2 infection. Thus, COVID-19 vaccination should be encouraged for pregnant individuals.

JAMA Pediatr. doi:10.1001/jamapediatrics.2022.3456
Published online October 3, 2022.

Supplemental content

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SARS-CoV-2 infection during pregnancy is associated with increased risks of maternal morbidity and adverse perinatal outcomes, such as hospitalization, intensive care unit admission, and death.[1,2] The association between COVID-19 infection in pregnancy and adverse neonatal events has also been reported, including preterm birth, stillbirth, and neonatal or perinatal morbidity.[3-5] Since the approval of COVID-19 messenger RNA (mRNA) vaccines, vaccination during pregnancy has been recommended to prevent illness in pregnant individuals and newborns.[6] However, vaccine hesitancy during pregnancy may still exist owing to safety concerns.[7,8]

Initial data on COVID-19 vaccines were limited because pregnant individuals were not included in the phase 3 trials of mRNA COVID-19 vaccines that were approved in the US and the European Union.[9,10] Preliminary studies for pregnant individuals did not show the increased risk of adverse neonatal outcomes, including miscarriage, preterm birth, small size for gestational age (SGA), and fetal/neonatal death, associated with mRNA COVID-19 vaccination.[11-13] In addition, emerging evidence from large epidemiological studies has indicated that COVID-19 vaccination during pregnancy was not associated with increased risks of adverse maternal and neonatal outcomes, such as miscarriage, preterm birth, and SGA.[14-17] Recently, 2 population-based observational studies from Canada and Sweden/Norway have provided further reassuring evidence regarding the safety of COVID-19 vaccination during pregnancy, using large cohort data on more than 250 000 pregnancies.[18,19] However, pooled evidence from large studies regarding neonatal and maternal outcomes of COVID-19 vaccination during pregnancy is scarce. Furthermore, comparative outcomes after COVID-19 vaccines in the first, second, or third trimester are unclear.

Therefore, we conducted a systematic review and meta-analysis to investigate neonatal and maternal outcomes associated with COVID-19 vaccination during pregnancy for a better understanding of the benefits and safety of COVID-19 vaccines in pregnant individuals.

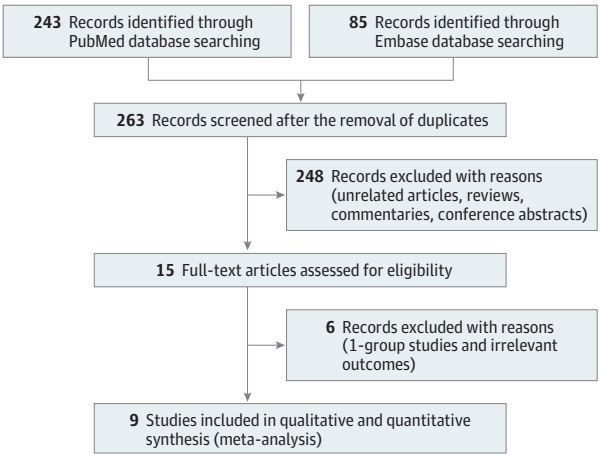
Key Points

Question Is COVID-19 vaccination during pregnancy associated with increased risks of peripartum adverse outcomes?

Findings In this systematic review and meta-analysis, COVID-19 vaccination during pregnancy was not associated with increased risks of peripartum adverse outcomes, including preterm birth, small size for gestational age, low Apgar score at 5 minutes, cesarean delivery, postpartum hemorrhage, and chorioamnionitis. Furthermore, COVID-19 vaccination during pregnancy was associated with lower risks of neonatal intensive care unit admission, intrauterine fetal death, and maternal SARS-CoV-2 infection.

Meaning In this study, COVID-19 vaccination appeared to be safe and beneficial to pregnant individuals.

Figure 1. Flowchart of Study Selection



Of the 263 identified articles, 9 studies comparing neonatal/maternal outcomes in individuals with vs without COVID-19 vaccination during pregnancy.

Methods

This research was conducted under Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines and registered in the International Prospective Register of Systematic Reviews (CRD42022323318).[20] Because our study does not include individual patient data, an informed consent waiver and an ethics exemption were granted.

Data Sources and Search

We used a 2-level strategy to search for all prospective trials and observational studies that investigated the neonatal outcomes in association with COVID-19 vaccination during pregnancy. First, a comprehensive literature search was conducted using the PubMed and EMBASE databases on April 5, 2022. The search terms included ("COVID-19" or "SARS-CoV-2") and ("vaccination" or "vaccine") and (during pregnancy) and ("neonates" or "neonatal," or "birth" or "baby"). Second, we performed an additional manual search of secondary sources, such as references of initially identified studies, to collect relevant articles comprehensively. No restrictions on language, publication date, and publication status were applied.

Eligibility Criteria

Studies meeting the following criteria were included in our review: (1) the study was published in a peer-reviewed journal, (2) the study compared pregnant individuals who received at least 1 COVID-19 vaccination during pregnancy with those who did not, (3) the study reported at least 1 of the following neonatal outcomes, preterm birth (delivery at <37 weeks' gestation), SGA (birth weight below the 10th percentile standardized for gestational age and sex), low Apgar score (Apgar score at 5 minutes <7), neonatal intensive care unit (NICU) admission, and intrauterine fetal death (IFD). Articles without original patient data (eg, guidelines, correspondence, research letters, and reviews) were excluded. The risk of bias of the included studies was evaluated using a tool for assessing risk of bias in nonrandomized studies (ROBINS).[21] The overall quality of each study was assessed using GRADE approach.[22]

Table 1. Baseline Characteristics

Source	Vaccination status	Country	Observational period	Cohort size, No.	Vaccine type, No. (2 doses during pregnancy)[a]	Vaccination timing, No.	Age, mean (SD), y	No. (%)				
								Nulliparous	Comorbidities[b]	Smoking history[c]	Obesity	Twins
Mayo et al,[24] 2021	Vaccinated	Israel	April 2020-June 2021	125	Vaccine type unavailable (125)	1st, 9; 2nd, 80; 3rd, 36	31.4 (6.1)	NA	HTN, 5 (4.0); diabetes, 9, (7.2); asthma, 1 (0.8); thyroid disease, 8 (6.4)	5 (4.0)	NA	NA
	Unvaccinated			369	NA	NA	29.5 (5.5)	NA	HTN, 12 (3.3); diabetes, 19 (5.1); asthma, 7 (1.9); thyroid disease, 14 (3.8)	11 (3.0)	NA	NA
Theiler et al,[25] 2021	Vaccinated	US	December 2020-April 2021	140	Pfizer-BioNTech, 127 (97), Moderna, 12 (6), Janssen/ Johnson & Johnson (1)	NA	31.8 (3.7)	56 (40)	HTN, 6 (4.3); diabetes, 2 (1.4); asthma, 15 (10.7); infertility, 6 (4.3)	0	33 (23.6)	2 (1.4)
	Unvaccinated			1862	NA	NA	30.5 (5.2)	546 (29.3)	HTN, 64 (3.4); diabetes, 11 (0.6); asthma, 206 (11.1); infertility, 14 (0.8)	196 (10.5)	464 (24.9)	22 (1.2)
Rottenstreich et al,[26] 2022	Vaccinated	Israel	January 2021-April 2021	712	Pfizer-BioNTech (712)	1st, 0; 2nd, 0; 3rd, 712	30.6 (5.8)	122 (17.1)	Previous miscarriage, 240 (33.7); HTN, 10 (1.4); diabetes, 45 (6.3); infertility, 33 (4.6)	NA	101 (14.2)	16 (2.2)
	Unvaccinated			1063	NA	NA	29.5 (6)	211 (19.8)	Previous miscarriage, 296 (27.8); HTN, 19 (1.8); diabetes, 45 (4.2); infertility, 24 (2.3)	NA	140 (13.2)	15 (1.4)
Lipkind et al,[17] 2022	Vaccinated	US	December 2020-July 2021	10 064	Pfizer-BioNTech, 5478, Moderna, 4162 (7881), Janssen/ Johnson & Johnson, 424	1st, 172; 2nd, 3668; 3rd, 6224	32.3 (4.5)	NA	HTN, 552 (5.5); diabetes, 167 (1.7); asthma, 802 (8.0); cancer, 28 (0.3); SLE, 20 (0.2); liver disease, 97 (1.0); cardiovascular disease, 43 (0.4);	1786 (17.7)	2407 (23.9)	0
	Unvaccinated			36 015	NA	NA	29.8 (5.3)	NA	HTN, 1732 (4.8); diabetes, 611 (1.7); asthma, 2733 (7.6); cancer, 120 (0.3); SLE, 103 (0.3); liver disease, 417 (1.2); cardiovascular disease, 104 (0.3)	7242 (20.1)	10 426 (28.9)	0

(continued)

Table 1. Baseline Characteristics (continued)

Source	Vaccination status	Country	Observational period	Cohort size, No.	Vaccine type, No. (2 doses during pregnancy)[a]	Vaccination timing, No.	Age, mean (SD), y	No. (%)				
								Nulliparous	Comorbidities[b]	Smoking history[c]	Obesity	Twins
Blakeway et al,[27] 2022	Vaccinated	United Kingdom	March 2021-April 2021	140	Pfizer-BioNTech, 109 (NA), Moderna, 18 (NA), AstraZeneca, 13	1st, 0; 2nd, 20; 3rd, 120	35 (31.7-37)	78 (55.7)	HTN, 13 (9.3); diabetes, 26 (18.6); cardiovascular disease, 1 (0.7)	1 (0.7)	15 (10.7)	4 (2.9)
	Unvaccinated			1188	NA	NA	Median (range), 33 (30-36)	593 (49.9)	HTN, 46 (3.9); diabetes, 153 (12.9); cardiovascular disease, 10 (0.8)	27 (2.3)	173 (14.6)	24 (2.0)
Goldshtein et al,[15] 2022	Vaccinated	Israel	March 2021-September 2021	16 697	Pfizer-BioNTech, 16 697 (NA)	1st, 2134; 2nd, 9364; 3rd, 5199	31.6 (5.2)	5555 (33.3)	HTN, 159 (1.0); diabetes, 145 (0.9); infertility, 304 (1.8); cancer, 168 (1.0); CKD, 118 (0.7)	798 (4.8)	1768 (10.6)	0
	Unvaccinated			7591	NA	NA	30.5 (5.7)	2484 (32.7)	HTN, 76 (1.0); diabetes, 59 (0.8); infertility, 84 (1.1); cancer, 55 (0.7); CKD, 67 (0.9)	441 (5.8)	862 (11.4)	0
Dick et al,[28] 2022	Vaccinated	Israel	December 2020-July 2021	2305	Pfizer-BioNTech, Moderna (NA)	1st, 12; 2nd, 964; 3rd, 1329	Median (range), 30 (26-34)	611 (26.5)	HTN, 25 (1.1); diabetes, 222 (9.6)	79 (3.4)	NA	0
	Unvaccinated			3313	NA	NA	Median (range), 30 (26-34)	838 (25.3)	HTN, 44 (1.3); diabetes, 275 (8.3)	88 (2.7)	NA	0
Fell et al,[18] 2022	Vaccinated	Canada	December 2020-September 2021	22 660	Pfizer-BioNTech, 18 101, Moderna, 4507 (21 894),[c] others, 52	NA	32.8 (4.3)	10 382 (46.1)	HTN, 202 (0.9); diabetes, 234 (1.0); asthma, 935 (4.1); thyroid disease, 1531 (6.8); cardiovascular disease, 43 (0.2)	723 (3.3)	4096 (20.0)	328 (1.4)
	Unvaccinated			74 930	NA	NA	32.0 (4.8)	31 965 (42.8)	HTN, 729 (3.2); diabetes, 836 (1.1); asthma, 2886 (3.9); thyroid disease, 3977 (5.3); cardiovascular disease, 66 (0.1)	5657 (7.7)	14 043 (21.1)	1064 (1.4)

(continued)

Data Extraction

Two investigators (A.W. and J.Y.) reviewed the search results separately to identify the studies based on the inclusion and exclusion criteria and assessed the eligibility for each study. After screening the articles based on title and abstract, we then retrieved the full texts of potentially eligible studies for further review. Disagreements were resolved through consensus or the third investigator (T.K.).

Data Items

Baseline characteristics, such as age, comorbidities, smoking status, the proportion of twins, obesity (BMI >30), and nulliparous were extracted. Regarding the COVID-19 vaccine, we collected the type of vaccine (eg, mRNA and viral vector), doses, and the timing of the first injection (first, second, and third trimester [<14 weeks, 14-28 weeks, and >28 weeks gestation, respectively]). The primary outcomes of this study were pre-

Table 1. Baseline Characteristics (continued)

Source	Vaccination status	Country	Observational period	Cohort size, No.	Vaccine type, No. (2 doses during pregnancy)[a]	Vaccination timing, No.	Age, mean (SD), y	No. (%)				
								Nulliparous	Comorbidities[b]	Smoking history[c]	Obesity	Twins
Magnus et al,[19] 2022	Vaccinated	Sweden	January 2021-January 2022	28 506	Pfizer-BioNTech, 20 424, Moderna, 7607 (21 580),[c] AstraZeneca, 475	1st, 1125; 2nd, 13 012; 3rd, 1468	32.2 (4.6)	12 450 (43.7)	HTN, 185 (0.6); diabetes, 417 (1.5); asthma, 2456 (8.6); CKD, 129 (0.5); cardiovascular disease, 433 (1.5); VTE, 219 (0.8)	657 (2.3)	NA	0
	Unvaccinated			129 015	NA	NA	30.5 (4.8)	54 306 (42.1)	HTN, 685 (0.5); diabetes, 1201 (0.9); asthma, 8826 (6.8); CKD, 627 (0.5); cardiovascular disease, 1563 (1.2); VTE, 775 (0.6)	5268 (4.1)	NA	0

Abbreviations: CKD, chronic kidney disease; HTN, hypertension; NA, not available; SLE, systemic lupus erythematosus; VTE, venous thromboembolism; 1st, during the first trimester; 2nd, during the second trimester; 3rd, during the third trimester.

[a] The total number of individuals who received the second dose of messenger RNA vaccines during pregnancy regardless of brands.

[b] Hypertension and diabetes include both pregestational and gestational conditions.

[c] Smoking history includes ever-smoker and smoking during pregnancy.

term birth, SGA, NICU admission, low Apgar score, and IFD. Secondary outcomes included maternal SARS-CoV-2 infection, postpartum hemorrhage, cesarean delivery, and chorioamnionitis. The definition of postpartum hemorrhage followed each study.

Data Synthesis and Analysis

The unadjusted and adjusted (whenever available) odds ratios (ORs) of each study were extracted. For studies that used propensity score analyses, we extracted the outcomes estimated by propensity score matching or inverse probability treatment weighting. The OR with a 95% CI of each outcome was calculated using the Review Manager (RevMan) version 5.4 (Nordic Cochrane Center, the Cochrane Collaboration) with a random-effects model. Heterogeneity was assessed using I^2, with more than 50% indicating substantial heterogeneity. As secondary analyses, we compared the frequency of preterm birth and SGA in the 2 subgroups: (1) pregnant individuals who received the first vaccination during the first trimester vs those who did not receive vaccination during pregnancy, (2) pregnant individuals who received the first vaccination during the second and third trimester vs those who did not receive vaccination during pregnancy. Publication bias was assessed by Egger linear regression tests and funnel plots of the primary outcomes in each study using ProMeta 3.0.[23]

Results

The study team identified 263 articles by the initial database search and subsequent manual search. After removing 248 items based on the title and abstract, the study team retrieved the full text of 15 articles. Six were excluded either because they did not have a comparison between vaccinated pregnant individuals and those unvaccinated or they reported irrelevant outcomes. Ultimately, the study team included 81 349 pregnant individuals who received at least 1 COVID-19 vaccination during pregnancy (vaccinated group) and 255 346 pregnant individuals who did not (unvaccinated group) from 9 observational studies[15,17-19,24-28] (**Figure 1**). The risk of bias assessment and the overall quality of each study were summarized in eFigure 1 and eTable 1 in the Supplement. The overall quality of evidence of the most studies was graded low or moderate level of certainty (**Table 1**).

Baseline Characteristics

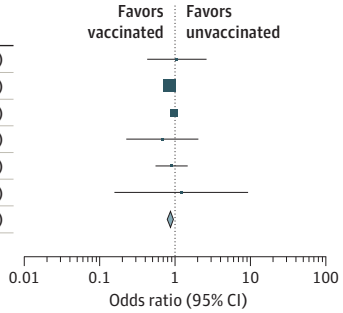
The mean or median age ranged from 32 to 35 years in the vaccinated group and from 29.5 to 33 years in the unvaccinated group. The proportion of comorbidities were as follows: pregestational/gestational diabetes, 1267 of 81 349 (1.6%) and 3210 of 255 346 (1.3%); pregestational/gestational hypertension, 1176 of 81 349 (1.4%) and 3632 of 255 346 (1.4%); obesity, 8420 of 48 231 (17.5%) and 26 108 of 114 355 (22.8%); smoking history, 4049 of 80 035 (5.1%) and 7.5% 18 930 of 252 990 (7.5%) in vaccinated and unvaccinated pregnant individuals, respectively. Nulliparous consisted 29 254 of 71 031 (41.2%) and 90 943 of 218 666 (41.6%) births in vaccinated and unvaccinated pregnant individuals, respectively. Of the included births, 350 of 81 224 (0.4%) vaccinated and 1125 of 254 997 (0.4%) unvaccinated pregnant individuals were nonsingletons. For vaccinated pregnant individuals, 98.2% received mRNA vaccines (Pfizer-BioNTech, 61 288; Moderna, 16 036; unstipulated, 2575), 1.1% received viral vector vaccine (AstraZeneca, 488; Janssen/

Figure 2. Forest Plots Showing the Odds Ratio (OR) of Neonatal Outcomes

A Neonatal intensive care unit admission

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Blakeway et al,[27] 2022	0.0488	0.4555	133	399	1.05 (0.43-2.56)	1.1
Fell et al,[18] 2022	−0.1863	0.0252	22660	74930	0.83 (0.79-0.87)	57.6
Magnus et al,[19] 2022	−0.0305	0.0555	28506	129015	0.97 (0.87-1.08)	36.4
Mayo et al,[24] 2021	−0.3857	0.5531	125	369	0.68 (0.23-2.01)	0.8
Rottenstreich et al,[26] 2022	−0.1054	0.2421	712	1063	0.90 (0.56-1.45)	3.9
Theiler et al,[25] 2021	0.1906	1.0323	140	1862	1.21 (0.16-9.15)	0.2
Total (95% CI)			52276	207638	0.88 (0.80-0.97)	100.0

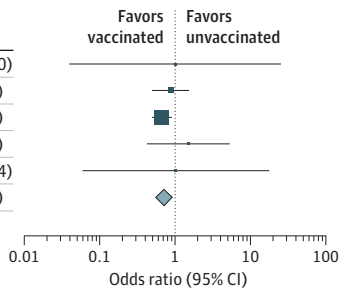
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.07$; $df = 5$ ($P = .22$); $I^2 = 29\%$
Test for overall effect: $z = 2.53$ ($P = .01$)



B Intrauterine fetal death

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Blakeway et al,[27] 2022	0	1.6423	133	399	1.00 (0.04-25.00)	0.6
Dick et al,[28] 2022	−0.1393	0.2826	2305	3313	0.87 (0.50-1.51)	20.6
Magnus et al,[19] 2022	−0.4005	0.1493	28506	129015	0.67 (0.50-0.90)	73.9
Rottenstreich et al,[26] 2022	0.4055	0.6375	712	1063	1.50 (0.43-5.23)	4.1
Theiler et al,[25] 2021	0.0198	1.4455	140	1862	1.02 (0.06-17.34)	0.8
Total (95% CI)			31796	135652	0.73 (0.57-0.94)	100.0

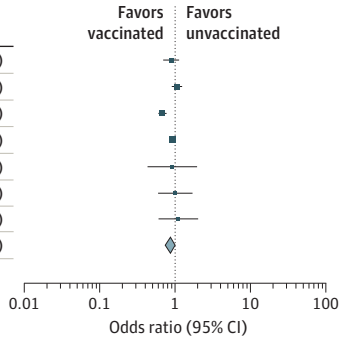
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.08$; $df = 4$ ($P = .72$); $I^2 = 0\%$
Test for overall effect: $z = 2.40$ ($P = .02$)



C Preterm birth

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Dick et al,[28] 2022	−0.1165	0.1153	2305	3313	0.89 (0.71-1.12)	16.6
Goldshtein et al,[15] 2022	0.0583	0.0723	16697	7591	1.06 (0.92-1.22)	20.8
Lipkind et al,[17] 2022	−0.3857	0.0554	10064	36015	0.68 (0.61-0.76)	22.3
Magnus et al,[19] 2022	−0.1054	0.0352	28506	129015	0.90 (0.84-0.96)	23.8
Mayo et al,[24] 2021	−0.0834	0.3763	125	369	0.92 (0.44-1.92)	3.9
Rottenstreich et al,[26] 2022	0.01	0.2573	712	1063	1.01 (0.61-1.67)	7.1
Theiler et al,[25] 2021	0.0953	0.3008	140	1862	1.10 (0.61-1.98)	5.6
Total (95% CI)			58549	179228	0.89 (0.76-1.04)	100.0

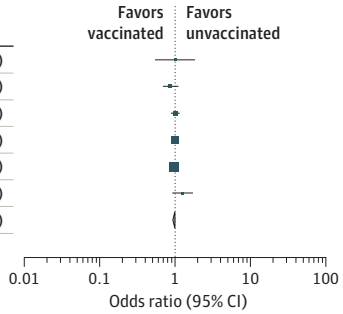
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 29.14$; $df = 6$ ($P < .001$); $I^2 = 79\%$
Test for overall effect: $z = 1.42$ ($P = .16$)



D Small size for gestational age

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Blakeway et al,[27] 2022	0	0.305	133	399	1.00 (0.55-1.82)	0.6
Dick et al,[28] 2022	−0.1393	0.1109	2305	3313	0.87 (0.70-1.08)	4.9
Goldshtein et al,[15] 2022	0.01	0.0588	16697	7591	1.01 (0.90-1.13)	17.4
Lipkind et al,[17] 2022	0	0.0425	8928	31699	1.00 (0.92-1.09)	33.3
Magnus et al,[19] 2022	−0.0305	0.0382	28506	129015	0.97 (0.90-1.05)	41.2
Rottenstreich et al,[26] 2022	0.2311	0.1549	712	1063	1.26 (0.93-1.71)	2.5
Total (95% CI)			57281	173080	0.99 (0.94-1.04)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.24$; $df = 5$ ($P = .52$); $I^2 = 0\%$
Test for overall effect: $z = 0.48$ ($P = .63$)



COVID-19 vaccination during pregnancy was associated with lower risks of neonatal intensive care unit admission and intrauterine fetal death. There were no associations between COVID-19 vaccination during pregnancy and preterm birth and small size for gestational age. ORs were calculated using random-effects model.

Johnson & Johnson, 425), and 0.7% were not clearly documented. Six studies reported the number of doses; 52 295 of 61 255 (85.4%) received 2 doses of mRNA vaccines during pregnancy. Seven studies reported the timing of the first vaccina-

Table 2. Neonatal Outcomes and the Timing of the First COVID-19 Vaccination

Outcomes	No.		OR (95% CI)
	Vaccinated during pregnancy	Unvaccinated during pregnancy	
Preterm birth			
1st Trimester vs unvaccinated	3443	171 927	1.81 (0.94-3.46)
2nd & 3rd Trimester vs unvaccinated	54 218	171 927	0.875 (0.63-0.90)
SGA			
1st Trimester vs unvaccinated	3249	165 741	1.09 (0.95-1.27)
2nd & 3rd Trimester vs unvaccinated	52 000	165 741	0.94 (0.88-1.00)

Abbreviations: OR, odds ratio; SGA, small for gestational age.

tion; 3452 of 58 548 (5.9%), 27 108 of 58 548 (46.3%), and 27 988 of 58 548 (47.8%) of the pregnant individuals received the first injection during the first, second, and third trimester, respectively.

Neonatal Outcomes

The COVID-19 vaccination during pregnancy was associated with lower risks of NICU admission (OR, 0.88; 95% CI, 0.80-0.97) and IFD (OR, 0.73; 95% CI, 0.57-0.94) (**Figure 2** A and B). The other primary outcomes did not show statistically significant differences between the 2 groups: preterm birth (OR, 0.89; 95% CI 0.76-1.04), SGA (OR, 0.99; 95% CI, 0.94-1.04) (Figure 2C and D), and low Apgar score (OR, 0.94; 95% CI, 0.87-1.02) (eFigure 3 in the Supplement). The outcome of each study is summarized in eTable 2 in the Supplement. Significant publication bias was not detected (eTable 3 and eFigure 2 in the Supplement), although the Egger test did not have enough power to fully detect the publication bias because the study team included only 9 studies.

Four studies separately reported the incidence of preterm birth and SGA according to the time of the first vaccination.[15,17,19,28] Between the pregnant individuals who received the first vaccination during the first trimester vs those who did not receive COVID-19 vaccination during pregnancy, the incidence of preterm birth (OR, 1.81; 95% CI, 0.94-3.46) and SGA (OR, 1.09; 95% CI, 0.95-1.27) were not significantly different (**Table 2** ; eFigures 4 and 5 in the Supplement). In contrast, COVID-19 vaccination during the second or third trimester was associated with lower risks of preterm birth (OR, 0.80; 95% CI, 0.69-0.92) and SGA (OR, 0.94; 95%, CI 0.88-1.00) vs those who did not receive COVID-19 vaccination during pregnancy (eFigures 5 and 6 in the Supplement).

Maternal Outcomes

The COVID-19 vaccination during pregnancy was significantly associated with a lower risk of maternal SARS-CoV-2 infection over the follow-up periods (OR, 0.46; 95% CI, 0.22-0.93) (**Figure 3** A). In contrast, the COVID-19 vaccinations during pregnancy were not associated with higher risks of cesarean delivery (OR, 1.05; 95% CI, 0.93-1.20), postpartum hemorrhage (OR, 0.95; 95% CI, 0.83-1.07) (the definition in each study is available in eTable 4 in the Supplement), and chorioamnionitis (OR, 1.06; 95% CI, 0.86-1.31) (Figure 3B-D).

Discussion

In this meta-analysis of 9 studies including 81 349 pregnant individuals who received COVID-19 vaccination during pregnancy and 255 346 of those who did not, we demonstrated that COVID-19 vaccination was not associated with increased risk of neonatal and maternal adverse outcomes, regardless of the timing of the first dose.

COVID-19 vaccination during pregnancy was not associated with increased risks of neonatal outcomes, including preterm birth, SGA, and low Apgar score. Furthermore, it was associated with lower risks of NICU admission and IFD. This positive association between COVID-19 vaccination during pregnancy and neonatal outcomes is plausible because SARS-CoV-2 infection in pregnant individuals may be associated with higher risks of NICU admission, IFD, and perinatal mortality.[4,5] According to previous multicenter studies, the COVID-19 severity appeared to be related to worse maternal and neonatal outcomes.[4,29] In particular, since most pregnant individuals with COVID-19 who required intensive care were unvaccinated,[29] maternal protection against SARS-CoV-2 is paramount. Moreover, it should also be noted that even asymptomatic SARS-CoV-2 infection was associated with higher risks of maternal outcomes, including preeclampsia and preterm labor.[4] Given the promising efficacy of COVID-19 vaccination in preventing maternal SARS-CoV-2 infection and the critical association between COVID-19 and neonatal/maternal outcomes, our findings further underlined the importance of maternal protection against SARS-CoV-2 infection.

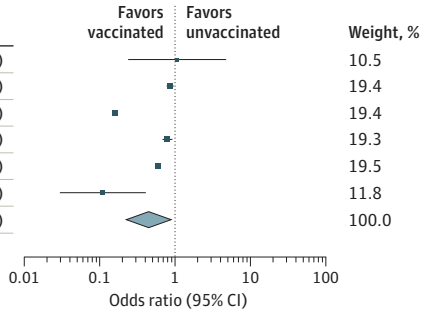
In addition, a recent study showed that COVID-19 vaccination during early pregnancy was not associated with an increased risk of ultrasound-detectable congenital fetal structural anomalies. They detected fetal anomalies in 27 of 534 unvaccinated pregnant individuals (5.1%) and 109 of 2622 pregnant individuals (4.2%) who received at least 1 dose of vaccine and suggested no significant risk of congenital fetal anomalies stratified by COVID-19 vaccine exposure within teratogenic periods, although the generalizability of this quaternary center's finding may be limited.[30] Notwithstanding, their data were compatible with our results, showing no significant difference in the risk of preterm birth between COVID-19 vaccination during the first trimester vs nonvaccination. Our meta-analysis could contribute to establishing the safety of COVID-19

Figure 3. Forest Plots Showing the Odds Ratio (OR) of Maternal Outcomes

A SARS-CoV-2 infection

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Blakeway et al,[27] 2022	0.0583	0.7566	140	1188	1.06 (0.24-4.67)	10.5
Fell et al,[18] 2022	−0.1508	0.0433	22660	74930	0.86 (0.79-0.94)	19.4
Goldshtein et al,[15] 2022	−1.8326	0.0329	16697	7591	0.16 (0.15-0.17)	19.4
Lipkind et al,[17] 2022	−0.2357	0.0691	10064	36015	0.79 (0.69-0.90)	19.3
Magnus et al,[19] 2022	−0.5108	0.0262	28506	129015	0.60 (0.57-0.63)	19.5
Theiler et al,[25] 2021	−2.2073	0.6629	140	1862	0.11 (0.03-0.40)	11.8
Total (95% CI)			78207	250601	0.46 (0.22-0.93)	100.0

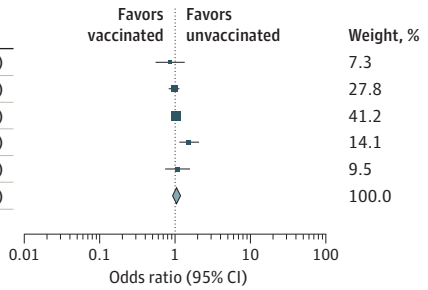
Heterogeneity: $\tau^2 = 0.67$; $\chi^2 = 1402.64$; $df = 5$ ($P < .001$); $I^2 = 100\%$
Test for overall effect: $z = 2.16$ ($P = .03$)



B Cesarean delivery

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Blakeway et al,[27] 2022	−0.1508	0.2189	133	399	0.86 (0.56-1.32)	7.3
Dick et al,[28] 2022	−0.0305	0.0734	2305	3313	0.97 (0.84-1.12)	27.8
Fell et al,[18] 2022	0.01	0.0206	22660	74930	1.01 (0.97-1.05)	41.2
Rottenstreich et al,[26] 2022	0.4187	0.1423	712	1063	1.52 (1.15-2.01)	14.1
Theiler et al,[25] 2021	0.077	0.186	140	1862	1.08 (0.75-1.56)	9.5
Total (95% CI)			25950	81567	1.05 (0.93-1.20)	100.0

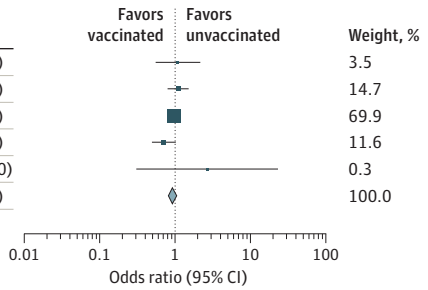
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 9.17$; $df = 4$ ($P = .06$); $I^2 = 56\%$
Test for overall effect: $z = 0.78$ ($P = .43$)



C Postpartum hemorrhage

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Blakeway et al,[27] 2022	0.0862	0.3398	133	399	1.09 (0.56-2.12)	3.5
Dick et al,[28] 2022	0.0953	0.1561	2305	3313	1.10 (0.81-1.49)	14.7
Fell et al,[18] 2022	−0.0513	0.0449	22660	74930	0.95 (0.87-1.04)	69.9
Rottenstreich et al,[26] 2022	−0.3425	0.1789	712	1063	0.71 (0.50-1.01)	11.6
Theiler et al,[25] 2021	0.9821	1.0986	140	1862	2.67 (0.31-23.00)	0.3
Total (95% CI)			25950	81567	0.95 (0.83-1.07)	100.0

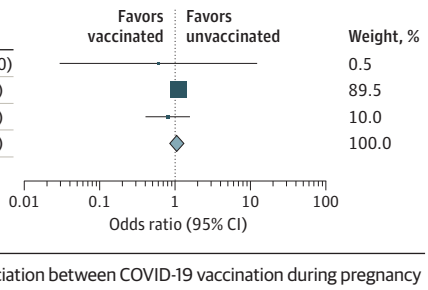
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.58$; $df = 4$ ($P = .33$); $I^2 = 13\%$
Test for overall effect: $z = 0.85$ ($P = .39$)



D Chorioamnionitis

Study or subgroup	log (Odds ratio)	SE	Vaccinated total	Unvaccinated total	Odds ratio (95% CI)	Weight, %
Blakeway et al,[27] 2022	−0.5108	1.5285	133	399	0.60 (0.03-12.00)	0.5
Fell et al,[18] 2022	0.0953	0.1139	22660	74930	1.10 (0.88-1.38)	89.5
Rottenstreich et al,[26] 2022	−0.2231	0.3411	712	1063	0.80 (0.41-1.56)	10.0
Total (95% CI)			23505	76392	1.06 (0.86-1.31)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.92$; $df = 2$ ($P = .63$); $I^2 = 0\%$
Test for overall effect: $z = 0.56$ ($P = .57$)



COVID-19 vaccination was associated with a lower risk of maternal SARS-CoV-2 infection. There was no association between COVID-19 vaccination during pregnancy and cesarean delivery, postpartum hemorrhage, and chorioamnionitis. ORs were calculated using random-effects model.

vaccines during pregnancy for newborns and will serve a critical role when counseling pregnant patients regarding the COVID-19 vaccination's teratogenicity.

Our study also demonstrated that COVID-19 vaccination during pregnancy was not associated with adverse maternal outcomes, including cesarean delivery, postpartum hemorrhage, and chorioamnionitis. Not surprisingly, COVID-19 vaccines exhibited a significant association with a decreased risk of maternal SARS-CoV-2 infection. Two doses of COVID-19 vaccines have been shown to induce comparable immune responses in pregnant individuals vs nonpregnant individuals.[31] Likewise, COVID-19 vaccines have provided high protection against documented SARS-CoV-2 infection in pregnant individuals.[32] Moreover, no evidence has been shown indicating an associated with increased risk of miscarriage after COVID-19 vaccination during early pregnancy.[14,16] These find-

ings support both the safety and effectiveness of COVID-19 vaccination during pregnancy for pregnant individuals.

Although emerging data have revealed the efficacy and safety of COVID-19 vaccination during pregnancy in neonatal and maternal outcomes, vaccination rates among pregnant individuals remain low worldwide.[33] Increasing vaccination rates in pregnant individuals are of paramount importance because they are at high risk for maternal morbidity and adverse perinatal outcomes. However, many pregnant individuals hesitate to receive COVID-19 vaccination despite global vaccination campaigns.[29] The previous studies reported that unvaccinated individuals against SARS-CoV-2 vaccination during pregnancy were more likely to be younger and non-White, smoke during pregnancy, use illicit drugs, have a lower income, and have a lower proportion of higher education.[18,19,25,26,28] Vaccine communication comprising education and recommendations can increase COVID-19 vaccine acceptance among pregnant individuals, as reported for tetanus-diphtheria-pertussis and influenza vaccines.[34,35] Additionally, our findings are reassuring and encouraging for pregnant individuals to consider COVID-19 vaccination. Although vaccinated and unvaccinated populations were not precisely matched, our findings should be widely disseminated to address the disparity and vaccine hesitancy. Further studies with tailored strategies are needed to validate our findings and achieve the acceptance of COVID-19 vaccines.

Although a recent study revealed the efficacy of vaccination against SARS-CoV-2 among adolescents,[36] there still remains hesitancy against vaccination among adolescents or reproductive ages.[8] However, our data support the safety and efficacy of COVID-19 vaccination during pregnancy, facilitating the vaccination rates among pregnant individuals even if they do not get vaccinated before pregnancy.

Limitations

This study had several limitations. First, no clear distinction could be made between emergency and scheduled procedures for cesarean delivery and preterm birth from available data. Although clinical indications for emergency cesarean delivery (eg, placental abruption, hypertensive disorders of pregnancy, and preterm prelabor rupture of membranes) differ from elective procedures, only 1 study reported them separately.[18] Further studies distinguishing this factor are warranted. Second, maternal obstetric histories were not extensively available. While more than half of the included individuals were multiparous, histories of previous cesarean delivery, hypertensive disorders of pregnancy, gestational diabetes, postpartum hemorrhage, miscarriage, preterm birth, and SGA were unobtainable, leading to the uncertainty of the baseline perinatal maternal risks. Third, the outcomes according to the timing of COVID-19 vaccination were not always reported in the included studies. As the number of vaccinated individuals during the first trimester was low, the results should be interpreted with caution. However, combining the existing publications allowed for a reliable analysis and provided no significant increased risk of neonatal and maternal outcomes associated with COVID-19 vaccination during the first trimester. Fourth, we could not assess the effect of variant types of SARS-CoV-2, such as Delta or Omicron, which may affect the effectiveness of COVID-19 vaccination.[37,38] Fifth, since all included articles were observational studies, our meta-analysis does not confirm the effect of COVID-19 vaccination in randomly assigned cohorts. Additionally, despite the vaccines' placental transportability and possible protective effect for newborns against SARS-CoV-2, long-term outcomes remain unelucidated.[39] Further large cohort studies with longer follow-up periods will help investigate long-term outcomes of COVID-19 vaccination during pregnancy.

Conclusions

In this systematic review and meta-analysis, COVID-19 vaccination during pregnancy was not associated with increased adverse peripartum outcomes. Our findings suggest that COVID-19 vaccination during pregnancy is safe and beneficial to mothers and newborns.

ARTICLE INFORMATION

Accepted for Publication: July 19, 2022.

Published Online: October 3, 2022. doi:10.1001/jamapediatrics.2022.3456

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Conflict of Interest Disclosures: None reported.

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