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Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes

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IMPORTANCE There is limited comparative epidemiological evidence on outcomes associated with COVID-19 vaccination during pregnancy; monitoring pregnancy outcomes in large populations is required.

OBJECTIVE To evaluate peripartum outcomes following COVID-19 vaccination during pregnancy.

DESIGN, SETTING, AND PARTICIPANTS Population-based retrospective cohort study in Ontario, Canada, using a birth registry linked with the provincial COVID-19 immunization database. All births between December 14, 2020, and September 30, 2021, were included.

EXPOSURES COVID-19 vaccination during pregnancy, COVID-19 vaccination after pregnancy, and no vaccination.

MAIN OUTCOMES AND MEASURES Postpartum hemorrhage, chorioamnionitis, cesarean delivery (overall and emergency cesarean delivery), admission to neonatal intensive care unit (NICU), and low newborn 5-minute Apgar score (<7). Linear and robust Poisson regression was used to generate adjusted risk differences (aRDs) and risk ratios (aRRs), respectively, comparing cumulative incidence of outcomes in those who received COVID-19 vaccination during pregnancy with those vaccinated after pregnancy and those with no record of COVID-19 vaccination at any point. Inverse probability of treatment weights were used to adjust for confounding.

RESULTS Among 97 590 individuals (mean [SD] age, 31.9 [4.9] years), 22 660 (23%) received at least 1 dose of COVID-19 vaccine during pregnancy (63.6% received dose 1 in the third trimester; 99.8% received an mRNA vaccine). Comparing those vaccinated during vs after pregnancy (n = 44 815), there were no significantly increased risks of postpartum hemorrhage (incidence: 3.0% vs 3.0%; aRD, −0.28 per 100 individuals [95% CI, −0.59 to 0.03]; aRR, 0.91 [95% CI, 0.82-1.02]), chorioamnionitis (0.5% vs 0.5%; aRD, −0.04 per 100 individuals [95% CI, −0.17 to 0.09]; aRR, 0.92 [95% CI, 0.70-1.21]), cesarean delivery (30.8% vs 32.2%; aRD, −2.73 per 100 individuals [95% CI, −3.59 to −1.88]; aRR, 0.92 [95% CI, 0.89-0.95]), NICU admission (11.0% vs 13.3%; aRD, −1.89 per 100 newborns [95% CI, −2.49 to −1.30]; aRR, 0.85 [95% CI, 0.80-0.90]), or low Apgar score (1.8% vs 2.0%; aRD, −0.31 per 100 newborns [95% CI, −0.56 to −0.06]; aRR, 0.84 [95% CI, 0.73-0.97]). Findings were qualitatively similar when compared with individuals who did not receive COVID-19 vaccination at any point (n = 30 115).

CONCLUSIONS AND RELEVANCE In this population-based cohort study in Ontario, Canada, COVID-19 vaccination during pregnancy, compared with vaccination after pregnancy and with no vaccination, was not significantly associated with increased risk of adverse peripartum outcomes. Study interpretation should consider that the vaccinations received during pregnancy were primarily mRNA vaccines administered in the second and third trimester.

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Pregnant individuals are at higher risk for COVID-19 complications, including hospitalization, intensive care unit (ICU) admission, and death, compared with nonpregnant individuals.[1,2] Significantly higher rates of adverse pregnancy outcomes, such as preterm birth and stillbirth, have also been observed after SARS-CoV-2 infection.[3,4] Vaccination during pregnancy is routinely recommended to prevent morbidity and mortality in both pregnant individuals and newborns from other infectious diseases, such as influenza and pertussis.[5] Since COVID-19 vaccines became available, many countries have also adopted recommendations for COVID-19 vaccination during pregnancy[6,7] to prevent severe COVID-19 and related complications in this population. Given the lack of prelicensure data specific to this population, ongoing safety monitoring is important to rule out potential risks of adverse maternal, fetal, and newborn outcomes. Emerging evidence from large epidemiological studies, to date, has not indicated any significantly increased risks of spontaneous abortion,[8,9] preterm birth,[10,11] or small-for-gestational-age birth[10,11] after COVID-19 vaccination during pregnancy; however, there is limited evidence from large populations on other outcomes after COVID-19 vaccination during pregnancy.

In Ontario—Canada's most populous province with universal, publicly-funded health care and approximately 140 000 births each year—pregnant individuals were designated a priority population for COVID-19 vaccination in late April 2021.[12] The purpose of this study was to evaluate the association between COVID-19 vaccination during pregnancy with maternal and neonatal peripartum outcomes occurring just before, during, or after delivery.

Key Points

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

Findings In this population-based retrospective cohort study of 97 590 individuals in Ontario, Canada, COVID-19 vaccination during pregnancy, compared with vaccination after pregnancy and with no vaccination, was not significantly associated with increased risk of postpartum hemorrhage, chorioamnionitis, cesarean delivery, admission to neonatal intensive care unit, or low newborn 5-minute Apgar score.

Meaning COVID-19 vaccination during pregnancy was not significantly associated with an increased risk of adverse peripartum outcomes.

Methods

This study used routinely collected data by province-wide registries, and no additional data were collected from patients. The research ethics board of the Children's Hospital of Eastern Ontario granted ethics approval and waived informed consent. We followed standardized guidance for reporting observational studies.[13]

Study Design and Population

This population-based retrospective cohort study used the Better Outcomes Registry & Network Ontario birth registry[14] linked with the provincial COVID-19 immunization database (COVaxON). We identified all pregnancy records in the birth registry with a birth date or expected due date on or after December 14, 2020 (when the COVID-19 vaccination program began in Ontario[15]), and excluded ongoing pregnancies as of September 30, 2021, individuals who became pregnant less than 42 weeks before the end of the study period (ie, those with a last menstrual period after December 9, 2020) to avoid cohort truncation bias,[16] records with documented gestational age less than 20 weeks at birth, and pregnancy terminations (**Figure 1**).

Data Sources

The Better Outcomes Registry & Network Ontario Information System collects extensive information on all live births and stillbirths from more than 250 hospitals, birth centers, midwifery practice groups, and prenatal screening laboratories across Ontario.[14] Available data include maternal demographics, health behaviors, preexisting health problems, pregnancy history, obstetric complications, interventions, and birth outcomes. These data are collected from medical records, clinical forms, and patient interview.[14,17] Using the maternal postal code, we linked the study population to Statistics Canada's 2016 Census, to obtain information on rural/urban residence and neighborhood income, and to the Ontario Marginalization Index, which provides 4 area-based measures reflecting social and economic marginalization.[18] Using unique health card numbers, we deterministically linked the study population with COVID-19 vaccination records in COVaxON up to September 30, 2021. Information on vaccine product, number of doses, and date(s) of vaccination are reported directly into COVaxON at the time of immunization. In a sensitivity analysis, we also deterministically linked with the Public Health Case and Contact Management Solution[19] to ascertain laboratory-confirmed COVID-19 during pregnancy.

Measures

Exposure

Ontario's COVID-19 vaccination program began on December 14, 2020 (Pfizer-BioNTech [BNT162b2] became available on December 14, 2020; Moderna [mRNA-1273], December 28, 2020; and AstraZeneca [AZD1222], February 26, 2021).[20,21] Pregnant people in early priority groups, such as front-line clinicians, were immediately eligible for vaccination[22]; however, it was not offered to the general population of pregnant individuals until April 23, 2021, when pregnancy became prioritized in Ontario's vaccination program.[12] Due to a limited vaccine supply in Canada during the first half of 2021, extended dose intervals and heterologous vaccine products to complete a series were recommended, where necessary.[23,24]

We determined the gestational timing of doses received during pregnancy using vaccination dates from COVaxON and the estimated date of birth recorded in the birth registry. COVID-19 vaccination was considered to have occurred during pregnancy if 1 or more doses were administered between

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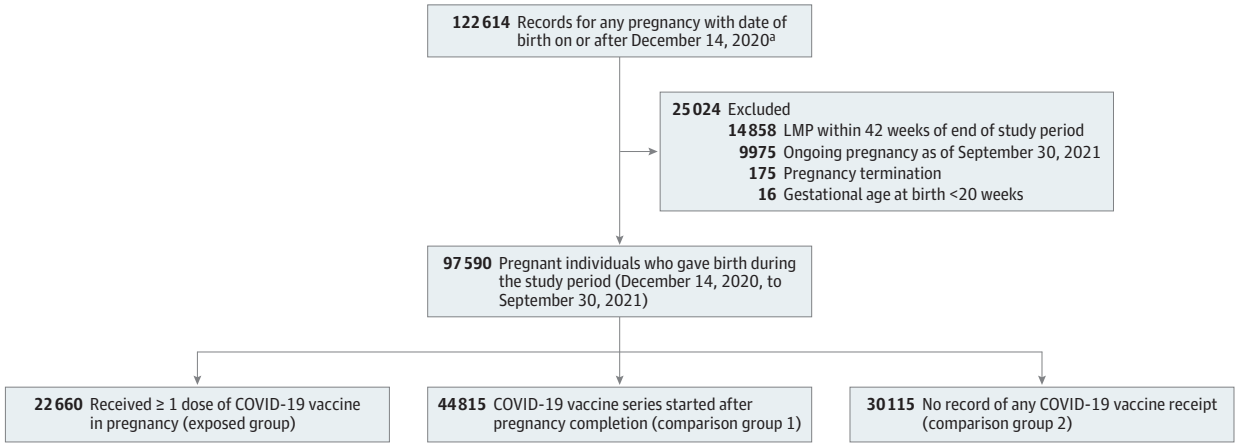
Figure 1. Flow of Individuals in a Study of the Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes



[a] These records represent all pregnant individuals (ie, 1 record per pregnant individual) and were used to evaluate obstetric outcomes (postpartum hemorrhage, chorioamnionitis, cesarean delivery, and emergency cesarean delivery).

the estimated date of conception up to 1 day before birth (conception date was estimated by adding 14 days to the last menstrual period date). Based on previous studies, we anticipated that baseline characteristics of individuals who were vaccinated during pregnancy would systematically differ from those who were unvaccinated during pregnancy.[25,26] Because vaccine eligibility and supply was limited in earlier study months, we hypothesized that individuals vaccinated after pregnancy would be more similar to those vaccinated during pregnancy than to those never vaccinated at any time. Therefore, we stratified the unvaccinated during pregnancy group into 2 comparison groups: (1) those vaccinated after pregnancy (comparison group 1) and (2) those with no record of any COVID-19 vaccination by September 30, 2021 (comparison group 2).

Outcomes

Assessing potential risks of vaccination during pregnancy requires careful consideration of the timing of vaccination relative to gestational exposure windows.[27] Because pregnant people were only prioritized for COVID-19 vaccination in late April 2021[12] and the study period included births up to September 30, 2021, vaccinated pregnancies occurred later in calendar time (eFigure 1 in the Supplement) and the majority of individuals in this group were vaccinated during the third trimester (**Figure 2**). This precluded assessment of outcomes with earlier gestational onset, such as those related to abnormal placentation; thus, we evaluated peripartum outcomes occurring just before, during, or after delivery that could plausibly be associated with later pregnancy vaccination (ie, vaccination during the second or third trimester). Obstetric outcomes included postpartum hemorrhage, chorioamnionitis, cesarean delivery, and emergency cesarean delivery (indications in eTable 1 in the Supplement); newborn outcomes included neonatal ICU (NICU) admission and low newborn 5-minute Apgar score (<7).

Covariates

We included covariates potentially associated with pregnancy outcomes and vaccination behavior in propensity scores to account for confounding. Covariates obtained from the birth registry included maternal age at delivery (in years); prepregnancy body mass index; self-reported maternal smoking status and substance use during pregnancy; public health unit region; preexisting maternal health conditions (asthma, chronic hypertension, diabetes, heart disease, thyroid disease); parity; and multiple birth. Covariates obtained from the Canadian Census included rural/urban residence and neighborhood-level income quintile. Covariates obtained from the Ontario Marginalization Index included neighborhood-level quintiles for residential instability (family or housing instability), material deprivation (inability to access and attain basic material needs), dependency (receipt of income support), and ethnic concentration (geographic areas with high concentrations of recent immigrants and/or "visible minorities," defined by Statistics Canada as persons, other than Aboriginal peoples, who self-identify as "non-Caucasian" or "non-White," including individuals identifying as South Asian, Chinese, Black, Filipino, Arab, Latin American, Southeast Asian, West Asian, Korean, Japanese, or other).[18] See eAppendix 1 in the Supplement for details.

Statistical Analyses

The number of pregnancies was the unit of analysis for obstetric outcomes, while it was all live births (1 record per infant, including multiples) for newborn outcomes. We compared the distribution of all baseline characteristics in pregnant individuals across exposure groups using standardized differences; an absolute standardized difference less than 0.1 was considered indicative of balance across groups.[28]

Unadjusted cumulative incidence rates for all outcomes by exposure group were computed; we used linear and log

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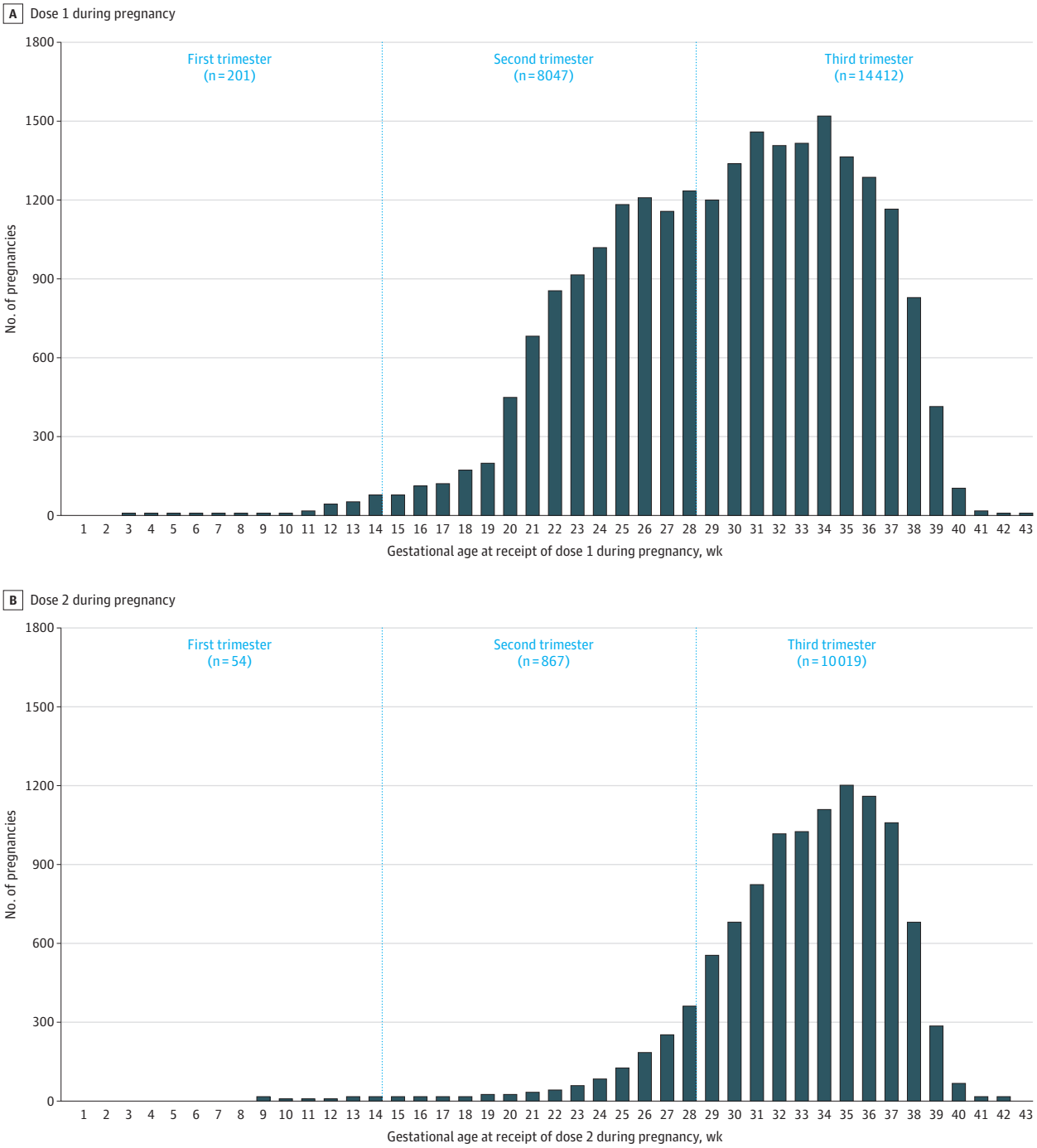
Figure 2. Gestational Age at COVID-19 Vaccination in a Study of the Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes



A, Median (IQR) gestational age at dose 1 was 213 (180-242) days. Counts for gestational weeks 2 and 3 have been combined to permit reporting (cell counts <6 cannot be reported). B, Median (IQR) gestational age at dose 2 was 238 (218-255) days. Counts for gestational weeks 2 to 9 have been combined to permit reporting (cell counts <6 cannot be reported).

Poisson regression (with robust variance estimation) to compute unadjusted risk differences (RDs) and risk ratios (RRs), respectively. Propensity score methods were used to account for potential confounding bias; 2 sets of propensity scores were computed, representing the predicted probability of COVID-19 vaccination during pregnancy relative to each comparison group. In addition to the variables listed previously, we included 2 temporal variables: calendar month of estimated conception and a flag denoting pregnancy completion prior to April 23, 2021. Multiple imputation was used to address missing

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covariate values (details about multiple imputation and propensity score methods provided in eAppendix 2 in the Supplement). Both sets of propensity scores were developed from each of the 5 imputed data sets and used to compute inverse probability of treatment weights, which were stabilized and trimmed to the first and 99th percentiles.[28]

Regression models incorporating stabilized weights from each of the imputed data sets were used to generate adjusted coefficients and standard errors, which were combined to produce adjusted estimates and 95% CIs. In subgroup analyses, we stratified by number of doses received during pregnancy, vaccine product received for dose 1, and trimester during which dose 1 was received. In sensitivity analyses, we applied alternate trimming values to the stabilized weights and ran conventional multivariable adjusted models instead of using weights. We also repeated the main analyses with additional adjustment for maternal age and calendar time (due to residual imbalances in these variables after weighting), time since vaccination (to account for gestational timing of vaccination), confirmed COVID-19 during pregnancy, and gestational age at birth. In addition, we carried out a post hoc assessment of the robustness of the propensity scores to the potential influence of calendar time due to changes in vaccine eligibility. Because of the potential for type I error due to multiple comparisons, findings should be interpreted as exploratory. Precision around point estimates was provided using 2-sided 95% CIs; estimates were considered statistically significant when the 95% CI excluded the null value. Analyses were conducted using SAS, version 9.4 (SAS Institute).

Results

There were 122 614 pregnant individuals in Ontario with a birth date or expected due date on or after December 14, 2020. There were 97 590 individuals remaining after exclusion of those who did not meet inclusion criteria (Figure 1), of whom 22 660 (23%) received at least 1 dose of COVID-19 vaccine during pregnancy and 74 930 (77%) had not been vaccinated by pregnancy completion (44 815 [46%] were vaccinated after pregnancy [comparison group 1] and 30 115 [31%] were not vaccinated at any point [comparison group 2]). The study flow diagram for newborn outcomes is provided in eFigure 2 in the Supplement.

Compared with individuals vaccinated after pregnancy (comparison group 1), those vaccinated during pregnancy were less likely to be younger than 30 years (23.7% vs 32.2%) and more likely to reside in neighborhoods with higher incomes (quintile 5: 21.3% vs 17.4%) and lower material deprivation (quintile 1: 28.6% vs 23.7%). Compared with individuals who were never vaccinated (comparison group 2), those vaccinated during pregnancy were more likely to reside in neighborhoods with higher incomes (quintile 5: 21.3% vs 13.1%) and lower material deprivation (quintile 1: 28.6% vs 16.9%) and were more likely to be nulliparous (46.1% vs 37.8%). They were also less likely to be younger than 30 years (23.7% vs 42.6%), smoke during pregnancy (3.3% vs 11.4%), and live in a rural setting (13.2% vs 18.3%) (**Table 1**). Following propensity score weighting, baseline characteristics were well-balanced across groups; all standardized differences, other than maternal age and calendar time, were less than 0.1 (eTable 3 and eFigure 3 in the Supplement) and there was adequate overlap in propensity score distributions by exposure group after weighting (eFigure 4 in the Supplement).

Of the 22 660 individuals vaccinated during pregnancy, 766 (3.4%) received only dose 1, 10 954 (48.3%) received dose 1 during pregnancy and dose 2 after pregnancy, and 10 940 (48.3%) received both doses during pregnancy. Overall, 63.6% of individuals vaccinated during pregnancy received dose 1 in the third trimester, at a median gestation of 213 days (30 weeks); 79.9% received BNT162b2 for dose 1, 19.9% received mRNA-1273, and less than 1% received another product (eTable 4 in the Supplement).

Compared with 44 815 individuals who initiated their COVID-19 vaccine series after pregnancy (comparison group 1), there was no significant association between COVID-19 vaccination during pregnancy and postpartum hemorrhage; the cumulative incidence of postpartum hemorrhage in both groups was 3.0%, the adjusted RR was 0.91 (95% CI, 0.82-1.02), and the adjusted RD was −0.28 per 100 individuals (95% CI, −0.59 to 0.03) (**Table 2**). COVID-19 vaccination during pregnancy was not significantly associated with a higher risk of chorioamnionitis (0.5% vs 0.5%; aRR, 0.92 [95% CI, 0.70-1.21]; aRD, −0.04 per 100 individuals [95% CI, −0.17 to 0.09]), cesarean delivery (30.8% vs 32.2%; aRR, 0.92 [95% CI, 0.89-0.95]; aRD, −2.73 per 100 individuals [95% CI, −3.59 to −1.88]), or emergency cesarean delivery (15.3% vs 16.4%; aRR, 0.89 [95% CI, 0.84-0.94]; aRD, −1.81 per 100 individuals [95% CI, −2.54 to −1.08]). Rates of adverse newborn outcomes were lower among those born to individuals vaccinated during pregnancy (Table 2); after adjustment for confounding, the significantly lower risk persisted for both NICU admission (11.0% vs 13.3%; aRR, 0.85 [95% CI, 0.80-0.90]; aRD, −1.89 per 100 newborns [95% CI, −2.49 to −1.30]) and low 5-minute Apgar score (<7) (1.8% vs 2.0%; aRR, 0.84 [95% CI, 0.73-0.97]; aRD, −0.31 per 100 newborns [95% CI, −0.56 to −0.06]). Compared with the 30 115 individuals who were never vaccinated (comparison group 2), there were no significantly increased risks of any of the outcomes in those vaccinated during pregnancy; most CIs included the null value, except for risk of emergency cesarean delivery (15.3% vs 14.2%; aRR, 0.91 [95% CI, 0.87-0.96]; aRD, −1.35 per 100 individuals [95% CI, −2.06 to −0.63]) and NICU admission (11.0% vs 12.8%; aRR, 0.92 [95% CI, 0.87-0.97]; aRD, −0.93 per 100 newborns [95% CI, −1.52 to −0.35]), which were both significantly lower among individuals who were vaccinated during pregnancy (**Table 3**).

Subgroup and Sensitivity Analyses

In subgroup analyses comparing individuals vaccinated during pregnancy with those vaccinated after pregnancy (comparison group 1), there were no statistically significant increases in study outcomes when those vaccinated during pregnancy were stratified by number of doses received, vaccine product, or trimester of vaccination for dose 1 (eTable 5 in the Supplement). Results from sensitivity analyses did not

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Table 1. Unweighted Distribution of Baseline Characteristics of the Study Population[a,b]

Characteristic	Received ≥1 dose of COVID-19 vaccine during pregnancy, No. (%) (n = 22 660)	Not vaccinated during pregnancy			
		Initiated COVID-19 vaccine series after pregnancy, No. (%) (n = 44 815)	Standardized difference[c]	Not vaccinated with COVID-19 vaccine at any time, No. (%) (n = 30 115)	Standardized difference[d]
Maternal age, y					
<25	914 (4.0)	3284 (7.3)	0.14	4224 (14.0)	0.35
25-29	4468 (19.7)	11 138 (24.9)	0.12	8606 (28.6)	0.21
30-34	10 344 (45.6)	18 528 (41.3)	0.09	10 230 (34.0)	0.24
35-39	5864 (25.9)	9831 (21.9)	0.09	5565 (18.5)	0.18
≥40	1070 (4.7)	2034 (4.5)	0.01	1490 (4.9)	0.01
Mean (SD)	32.8 (4.3)	32.0 (4.8)	0.15	31.0 (5.5)	0.31
Estimated date of conception					
Before June 2020	27 (0.1)	14 591 (32.6)	0.98	6644 (22.1)	0.75
June-July 2020	467 (2.1)	15 981 (35.7)	0.95	6530 (21.7)	0.64
August-September 2020	7367 (32.5)	8886 (19.8)	0.29	6660 (22.1)	0.23
October-November 2020	10 925 (48.2)	4511 (10.1)	0.92	7374 (24.5)	0.51
December 2020 or later	3874 (17.1)	846 (1.9)	0.54	2907 (9.7)	0.22
Gave birth before April 23[e]	542 (2.4)	32 051 (71.5)	2.05	13 789 (45.8)	1.18
Nulliparous	10 382/22 531 (46.1)	20 614/44 635 (46.2)	0.00	11 351/29 999 (37.8)	0.17
Multiple birth	328 (1.4)	656 (1.5)	0.00	408 (1.4)	0.01
Preexisting maternal medical condition[f,g]	2763 (12.2)	5121 (11.4)	0.02	2931 (9.7)	0.08
Thyroid disease	1531 (6.8)	2711 (6.0)	0.03	1266 (4.2)	0.11
Asthma	935 (4.1)	1675 (3.7)	0.02	1211 (4.0)	0.01
Diabetes	234 (1.0)	526 (1.2)	0.01	310 (1.0)	0.00
Chronic hypertension	202 (0.9)	452 (1.0)	0.01	277 (0.9)	0.00
Heart disease	43 (0.2)	30 (0.1)	0.03	36 (0.1)	0.02
Smoked during pregnancy	723/22 058 (3.3)	2277/44 044 (5.2)	0.10	3380/29 593 (11.4)	0.31
Substance use during pregnancy[h]	648/21 805 (3.0)	1629/42 344 (3.8)	0.04	2392/28 920 (8.3)	0.23
Maternal BMI ≥30.0	4096/20 478 (20.0)	8350/40 129 (20.8)	0.01	5693/26 507 (21.5)	0.02
Neighborhood median family income quintiles					
1 (lowest)	3497/22 542 (15.5)	8449/44 572 (19.0)	0.09	7740/29 354 (26.4)	0.26
2	4165/22 542 (18.5)	8903/44 572 (20.0)	0.04	6417/29 354 (21.9)	0.07
3	4837/22 542 (21.5)	9717/44 572 (21.8)	0.01	5987/29 354 (20.4)	0.04
4	5247/22 542 (23.3)	9729/44 572 (21.8)	0.03	5354/29 354 (18.2)	0.13
5 (highest)	4796/22 542 (21.3)	7774/44 572 (17.4)	0.10	3856/29 354 (13.1)	0.22
Rural residence	2991 (13.2)	5954/44 808 (13.3)	0.00	5425/29 629 (18.3)	0.13
Material deprivation quintile[i]					
1 (least deprived)	6388/22 333 (28.6)	10 496/44 200 (23.7)	0.11	4705/27 921 (16.9)	0.31
2	5092/22 333 (22.8)	9323/44 200 (21.1)	0.04	4958/27 921 (17.8)	0.15
3	4071/22 333 (18.2)	8350/44 200 (18.9)	0.02	5103/27 921 (18.3)	0.03
4	3642/22 333 (16.3)	7997/44 200 (18.1)	0.05	5572/27 921 (20.0)	0.06
5 (most deprived)	3140/22 333 (14.1)	8034/44 200 (18.2)	0.11	7583/27 921 (27.2)	0.29
History of COVID-19 infection during pregnancy	689 (3.0)	1582 (3.5)	0.03	1061 (3.5)	0.03
Gestational age at birth, mean (SD), wk	38.8 (1.6)	38.6 (1.8)	0.09	38.8 (1.8)	0.01
Birth weight, mean (SD), g	3368 (526.7)	3325 (563.3)	0.06	3351 (557.2)	0.03

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] For variables with missing values, data are presented as the numerator over the denominator of nonmissing values.

[b] Additional baseline characteristics are presented in the Supplement (eTable 2 in Supplement).

[c] Absolute standardized difference between those who received ≥1 dose of COVID-19 vaccine during pregnancy and those who initiated COVID-19 vaccine series after pregnancy. Standardized difference >0.10 indicates an imbalance in the distribution between these 2 groups.

[d] Absolute standardized difference between those who received ≥1 dose of COVID-19 vaccine during pregnancy and those who had not received any COVID-19 vaccine at any time. Standardized difference >0.10 indicates an imbalance in the distribution between these 2 groups.

[e] Captures timing of pregnancy relative to April 23, 2021; pregnant individuals were designated a high-priority population for COVID-19 vaccination on April 23, 2021.

[f] Composite of asthma, chronic hypertension, diabetes, heart disease, or thyroid disease. Sum of individual conditions does not equal the total number of individuals with any condition, because categories were not mutually exclusive.

[g] Includes individuals with any preexisting maternal medical condition.

[h] Self-reported cannabis, opioid, or alcohol use during pregnancy.

[i] Based on Canadian Census data. It refers to individuals and communities being unable to access and attain basic material needs and is closely connected to poverty.

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Table 2. Risk of Adverse Peripartum Outcomes Among Individuals Who Received at Least 1 Dose During Pregnancy Compared With Those Who Initiated COVID-19 Vaccine Series After Pregnancy

Outcome	No. (%)		Risk ratio (95% CI)		
	Received ≥1 dose of COVID-19 vaccine during pregnancy	Initiated COVID-19 vaccine series after pregnancy (comparison group 1)	Crude	Adjusted[a]	Adjusted risk difference per 100 (95% CI)[a]
Pregnant individuals with a live birth or stillbirth, No.	22 660	44 815			
Postpartum hemorrhage	677 (3.0)	1351 (3.0)	0.99 (0.90 to 1.09)	0.91 (0.82 to 1.02)	−0.28 (−0.59 to 0.03)
Chorioamnionitis	101 (0.5)	214 (0.5)	0.93 (0.74 to 1.18)	0.92 (0.70 to 1.21)	−0.04 (−0.17 to 0.09)
Cesarean delivery	6988 (30.8)	14 427 (32.2)	0.96 (0.93 to 0.99)	0.92 (0.89 to 0.95)	−2.73 (−3.59 to −1.88)
Emergency cesarean delivery	2829 (15.3)	5943 (16.4)	0.93 (0.89 to 0.98)	0.89 (0.84 to 0.94)	−1.81 (−2.54 to −1.08)
Liveborn infants, No.	22 746	44 943			
NICU admission	2508 (11.0)	5969 (13.3)	0.83 (0.79 to 0.87)	0.85 (0.80 to 0.90)	−1.89 (−2.49 to −1.30)
Low 5-min Apgar score (<7)[b]	403/22 334 (1.8)	894/44 344 (2.0)	0.89 (0.79 to 1.00)	0.84 (0.73 to 0.97)	−0.31 (−0.56 to −0.06)

Abbreviation: NICU, neonatal intensive care unit.

[a] Adjusted using stabilized inverse probability of treatment weights.

[b] The Apgar scoring system is a standardized method to assess the status of newborns immediately after birth. It comprises 5 components (skin color, heart rate, reflexes, muscle tone, and respiration), each of which is given a score of 0, 1, or 2 (with 10 being the highest possible score).

Table 3. Risk of Adverse Peripartum Outcomes Among Individuals Who Received at Least 1 Dose During Pregnancy Compared With Those Not Vaccinated With COVID-19 Vaccine at Any Time

Outcome	No. (%)		Risk ratio (95% CI)		
	Received ≥1 dose of COVID-19 vaccine during pregnancy	Not vaccinated with COVID-19 vaccine at any time (comparison group 2)	Crude	Adjusted[a]	Adjusted risk difference per 100 (95% CI)[a]
Pregnant individuals with a live birth or stillbirth, No.	22 660	30 115			
Postpartum hemorrhage	677 (3.0)	1008 (3.4)	0.89 (0.81 to 0.98)	0.90 (0.81 to 1.00)	−0.32 (−0.64 to −0.01)
Chorioamnionitis	101 (0.5)	90 (0.3)	1.49 (1.12 to 1.98)	1.20 (0.90 to 1.59)	0.07 (−0.04 to 0.19)
Cesarean delivery	6988 (30.8)	8583 (28.5)	1.08 (1.05 to 1.12)	0.97 (0.94 to 1.00)	−0.97 (−1.81 to −0.14)
Emergency cesarean delivery	2829 (15.3)	3548 (14.2)	1.08 (1.03 to 1.14)	0.91 (0.87 to 0.96)	−1.35 (−2.06 to −0.63)
Liveborn infants, No.	22 746	30 109			
NICU admission	2508 (11.0)	3852 (12.8)	0.86 (0.82 to 0.91)	0.92 (0.87 to 0.97)	−0.93 (−1.52 to −0.35)
Low 5-min Apgar score (<7)[b]	403/22 334 (1.8)	588/29 588 (2.0)	0.91 (0.80 to 1.03)	0.88 (0.77 to 1.01)	−0.23 (−0.47 to 0.02)

Abbreviation: NICU, neonatal intensive care unit.

[a] Adjusted using stabilized inverse probability of treatment weights.

[b] The Apgar scoring system is a standardized method to assess the status of newborns immediately after birth. It comprises 5 components (skin color, heart rate, reflexes, muscle tone, and respiration), each of which is given a score of 0, 1, or 2 (with 10 being the highest possible score).

qualitatively differ from the original results (eTable 6 in the Supplement). Results from subgroup analyses comparing individuals vaccinated during pregnancy with those never vaccinated (comparison group 2) were consistent with results from the main analyses (eTable 7 in the Supplement). The magnitude and direction of point estimates from sensitivity analyses were similar to the main analyses, with the exception of an increase in NICU admission among infants born to vaccinated individuals when adjusted for time since dose 1 (aRR, 1.16 [95% CI, 1.07-1.26]; eTable 8 in the Supplement). The post hoc assessment of alternate propensity score specifications yielded weighted distributions and standardized differences that were similar to those from original analyses, supporting the robustness of the propensity scores to the effect of calendar time (eFigure 5 in the Supplement).

Discussion

In this large population-based study that included more than 22 000 individuals who received at least 1 dose of COVID-19 vaccine during pregnancy, vaccination was not significantly associated with any increased risk of postpartum hemorrhage, chorioamnionitis, cesarean delivery, NICU admission, or low 5-minute Apgar score. The results were largely unchanged when stratified according to the number of doses

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received during pregnancy, vaccine product, or the trimester when dose 1 was received. Moreover, the interpretations did not change when the comparison group was individuals who were vaccinated after pregnancy (who were more similar to those vaccinated during pregnancy with respect to baseline characteristics, but had different calendar timing of pregnancy) or individuals who had not received a COVID-19 vaccine at any point by the end of September 2021 (who were more similar to those vaccinated during pregnancy with respect to calendar timing of pregnancy, but had different baseline characteristics). The results were robust to sensitivity analyses designed to account for potential residual confounding by factors such as maternal age, calendar time, time since vaccination, gestational length, and COVID-19 during pregnancy.

COVID-19 vaccine effectiveness has been shown to be high in pregnant people, similar to the general population.[29,30] Because COVID-19 vaccine–derived maternal antibodies cross the placenta,[31] vaccination during pregnancy could potentially protect newborns in the early months of life, similar to well-established benefits of influenza and pertussis vaccination during pregnancy.[32,33] Large epidemiological studies of COVID-19 vaccination during pregnancy available to date have not identified significantly increased risks of preterm birth or small-for-gestational-age birth overall[10,11] or when stratified by the number of doses received during pregnancy or trimester of vaccination (second or third trimester).[10] Miscarriage risk after COVID-19 vaccination during early pregnancy has been assessed by 2 large population-based case-control studies, neither of which found evidence of increased odds of spontaneous abortion associated with having received a COVID-19 vaccine; these conclusions remained unchanged regardless of number of doses received or mRNA vaccine product.[8,9] These findings are consistent with the large body of research on influenza and pertussis immunization during pregnancy, in which no significant associations with adverse maternal, fetal, or neonatal outcomes have been identified.[34-39]

Strengths of this study include the large number of individuals vaccinated during pregnancy. The data sources, which were population-based, limited potential selection bias and provided detailed information on clinical and sociodemographic variables. COVID-19 vaccination was ascertained through linkage with the database that captures all immunization events in Ontario, regardless of where they were received; thus, exposure misclassification is unlikely.

Limitations

This study has several limitations. First, the study relied on clinician-assigned outcome diagnoses recorded in the birth registry; therefore, misclassification of some outcomes is possible—particularly chorioamnionitis, which is difficult to diagnose, and postpartum hemorrhage, which may be incompletely documented. Assuming any outcome misclassification is nondifferential, estimates could be biased toward the null, potentially obscuring an increase in risk; however, given that these outcomes are uncommon and likely measured with high specificity, misclassification would have a small effect.[40] Second, given the observational nature of this study, causality cannot be inferred and findings should be interpreted cautiously. Despite achieving good balance of baseline covariates in weighted analyses, propensity score derivation was limited to variables available in the study databases. Third, although important potential confounders such as smoking, body mass index, and socioeconomic indicators were included, there was no information on other health-related behaviors such as influenza vaccination during recent seasons; thus, residual confounding remains possible. Fourth, there was an increase in risk of NICU admission in one sensitivity analysis; however, given the robustness of the results to all other sensitivity analyses, this may represent type I error due to the many statistical comparisons. Fifth, individuals in this study were predominantly vaccinated during the second and third trimesters; because pregnant people were only prioritized for COVID-19 vaccination in late April 2021, pregnancies with earlier gestational vaccination are still ongoing. As more individuals vaccinated earlier in pregnancy give birth (expected in late 2021/early 2022), other important obstetric and perinatal outcomes with earlier gestational origin and earlier gestational timing of vaccination during pregnancy will be evaluated.

Conclusions

In this population-based cohort study in Ontario, Canada, COVID-19 vaccination during pregnancy, compared with vaccination after pregnancy and with no vaccination, was not significantly associated with increased risk of adverse peripartum outcomes. Study interpretation should consider that the vaccinations received during pregnancy were primarily mRNA vaccines administered in the second and third trimester.

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